

NICKEL ALLERGY AND HAND ECZEMA IN FEMALES

A clinical and pathogenetic study with special references to
the importance of ingested nickel

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This thesis is based on the following papers which will be referred to by their roman numerals:

- I. Christensen, O.B. & Möller, H.: Nickel allergy and hand eczema. Contact Dermatitis 1: 129-135, 1975.
- II. Christensen, O.B.: Prognosis in nickel allergy and hand eczema. Contact Dermatitis. Accepted for publication.
- III. Christensen, O.B. & Möller, H.: External and internal exposure to the antigen in the hand eczema of nickel allergy. Contact Dermatitis 1: 136-141, 1975.
- IV. Christensen, O.B. & Möller, H.: Release of nickel from cooking utensils. Contact Dermatitis 4: 343-346, 1978.
- V. Christensen, O.B. & Lagesson, V.: Nickel concentration of blood and urine after oral administration. Annals of Clinical and Laboratory Science 11: 119-125, 1981.
- VI. Christensen, O.B., Lindström, C.G., Löfberg, H. & Möller, H.: Micromorphology and specificity of orally induced flare-up reactions in nickel sensitive patients. Acta Dermato-Venereologica (Stockholm). Accepted for publication.

CONTENTS

<u>INTRODUCTION</u>	5
Historical background	5
Incidence of nickel sensitivity	5
Prevalence of nickel sensitivity	5
Incidence of nickel sensitivity in patients with hand eczema	6
Incidence of hand eczema in nickel sensitive patients	6
Prevalence of hand eczema in nickel sensitive patients	6
Secondary eruptions in nickel sensitivity	6
Introductory conclusion	7
<u>AIMS OF THE STUDY</u>	7
<u>ECZEMA DEFINITIONS</u>	7
<u>MATERIAL AND METHODS</u>	8
Patients	8
Clinical evaluation	8
Internal nickel provocation	9
External nickel provocation	9
Registration of activation	9
Patch testing	9
Intracutaneous testing	9
Punch biopsies, fixation and staining	10
Direct immunofluorescence	10
Determination of serum IgE	10
pH measurements	10
Determination of nickel in water boiled in different types of saucepans	10
Determination of nickel in blood and urine	10
Statistics	11
<u>RESULTS AND DISCUSSION</u>	11
Diagnosis and history in nickel sensitive patients with hand eczema	11
Prognosis and unfavourable factors influencing the prognosis in nickel sensitive patients with hand eczema	13
Clinical reaction after internal and external nickel provocation	15
Release of nickel from stainless steel utensils	17
Nickel in food	18
Nickel concentration in blood and urine in connection with nickel ingestion	19
Micromorphology and specificity of patch test and hand eczema flare-up reactions	19
Treatment of nickel sensitive patients with hand eczema	20
<u>GENERAL SUMMARY</u>	21
<u>ACKNOWLEDGEMENTS</u>	22
<u>REFERENCES</u>	23
<u>PAPERS I - VI</u>	

INTRODUCTION

Historical background

The first case of nickel as a cause of contact dermatitis was reported by Blaschko (1889). Since then and until 1930 many cases of dermatitis in nickel platers were reported from different industrial centres (Schittenhelm & Stockinger 1925, Bulmer & Mackenzie 1926, Grön 1929, Du Bois 1931). The term "Nickelkrätze" is often used in these purely occupationally induced cases of dermatitis. The first patch test with nickel sulfate was performed by Schittenhelm & Stockinger in 1925. In the beginning of the 1930:s the first cases of nickel dermatitis produced by articles in daily use were reported. Rothman (1930) and Preininger (1934) reported a causal association to nickel containing coins, Lain (1931) and McAlester & McAlester (1931) to spectacle frames, Du Bois (1932) and Fox (1933) to wrist watches. Since these initial case reports several studies (Bonnievie 1939, Calnan 1956, Fisher & Shapiro 1956, Wilson 1956, Wagmann 1959, Marcussen 1959a) have shown that nickel dermatitis became rather frequent, and the cause changed from an occupationally induced dermatitis to a dermatitis predominantly induced by nickel plated personal items.

Incidence of nickel sensitivity

Bonnievie (1939), who patch tested 1273 patients with 5% NiSO₄, reported an incidence of 5.2%. Marcussen (1959a) showed that the incidence increased from 1.8 - 3.2% during the period 1936 - 1955, and indicated that the increase was correlated to the Danish import of nickel. Among all patients patch tested in 6 Scandinavian dermatology departments (Magnusson et al 1968) the incidence of positive nickel tests was 5.9%; the incidence in 6 European departments (Fregert et al 1969) was found to be 6.7%. From North America (N. Am. C. D. Group 1973) an incidence of 11% is reported. Incidences from 4.7 - 10.7% are reported from different countries (Epstein et al 1968, Kanan 1969, Rudzki & Kleniewska 1970, Black 1972, Burry et al 1973). Striking geographical differences are observed in the studies referred to. In the Malmö department an incidence of 14.3% among 621 patch tested patients was found during 1980. In most papers published it is regularly noted that the female to male preponderance is high, nickel allergy predominantly being a female allergy. In Malmö during 1980 the sex ratio F:M was 15:1.

Prevalence of nickel sensitivity

Recently, papers published from Scandinavia and U.S.A. clearly indicate that the prevalence of nickel sensitivity among females in the general population today is around 10% (Menné 1978, Prystowsky et al 1978, Kiefer 1979, Magnusson & Möller 1979, Peltonen 1979). Menné (1980) reported that the frequency of a history of metal sensitivity among a stratified sample of 2.500 females in the Danish population was found to be 18% in younger age groups and 11% in an older one.

Incidence of nickel sensitivity in patients with hand eczema

Patients with hand eczema were studied by Agrup (1969) and 12% of the women but none of the men were sensitive to nickel. Of 238 women with hand eczema Cronin (1972) found 21% sensitive to nickel compared to 285 women having eczema elsewhere of whom 12% were nickel sensitive. Wilkinson et al (1970) reported in an European joint study that 11% of the women with hand eczema were nickel sensitive compared to 9% nickel sensitive without hand eczema.

Incidence of hand eczema in nickel sensitive patients

The incidence of hand eczema in nickel sensitive patients together with sex ratio, when reported, is listed in the table.

Nickel sensitive	Hand eczema %	Report
64 (58 ♀, 6 ♂)	50	Bonnevie 1939
81 ♀	20	Calnan 1956
85 ♀	17	Wilson 1956
40 (36 ♀, 4 ♂)	40	Fisher & Shapiro 1956)
621 (552 ♀, 69 ♂)	43	Marcussen 1960
62 ♀	35	Wagmann 1959
84 ♀	60	Cronin 1972
53 (49 ♀, 4 ♂)	47	Wahlberg & Skog 1971)
90 (sex ratio not stated)	56	Peltonen 1979

Prevalence of hand eczema in nickel sensitive patients

By testing 980 volunteers in the Finnish general population Peltonen (1979) found a simultaneously occurring hand eczema in 20% of the nickel sensitive patients, but 45% reported a present or previous hand eczema. In an interview examination by Menné (1978) 25% of nickel sensitive patients had had hand eczema. In an extended interview study comprising 2.500 of a stratified sample of Danish females (Menné 1980), he reported that hand eczema had occurred in 40% of nickel sensitive patients, but only in 19% in a control group.

Secondary eruptions in nickel sensitivity

Calnan (1956) and later Marcussen (1957) and Wagmann (1959) differentiated between primary and secondary eruptions in nickel allergy. The secondary spread was found in about 75% of patients with suspender dermatitis, and in 35% when the primary site was the ears or elsewhere. In most patients the spread was a papular or maculopapular rash usually located in the antecubital fossae, eyelids, sides of neck and inner thighs. In a few cases the rash became generalized. Not seldom secondary eruptions occurred without

a flare of a primary site. Even non-eczematous reactions as erythema multiforme, urticaria and generalized pruritus are described in nickel sensitive patients. The mechanisms of these secondary eruptions were debated and it was suggested that the spread was haematogenic and/or eczematid like (Calnan 1956, Wagmann 1959).

Introductional conclusion

Assessed from the investigations mentioned above it is clear that patients with nickel allergy comprise a considerable and probably increasing clinical problem, and today nickel is by far the most common hapten inducing contact allergy. The problem is obviously of a higher dignity, when nickel allergy and hand eczema coexist. In most reports dealing with nickel allergy and hand eczema a clinical description of the type of hand eczema is lacking or sparse and the pathogenesis of the hand eczema as well as the secondary eruptions commonly observed in nickel sensitive patients is often discussed. A reexamination of these conditions is therefore warranted.

AIMS OF THE STUDY

The purposes of the present investigation were as follows:

To describe the detailed clinical picture in nickel sensitive females with hand eczema.

To evaluate the prognosis in nickel sensitive females with hand eczema.

To estimate the clinical effect of internal and external provocation with nickel in nickel sensitive patients with hand eczema.

To seek sources of nickel contamination in our food, especially release of nickel from different types of cooking utensils.

To determine the nickel concentration in blood and nickel urine excretion following ingestion of a soluble nickel salt.

To investigate specificity and micromorphology of orally provoked flare-up reactions in nickel sensitive patients with hand eczema.

ECZEMA DEFINITIONS

Contact dermatitis type A ("Allergic contact eczema")

A recurring itching dermatitis with red papules and/or vesicles, localized on the dorsal aspects of hands and fingers, and the sides of fingers, sometimes extending to wrists and arms.

Contact dermatitis type B ("irritant dermatitis")

A more continuous dermatitis, reddish and scaling, often with painful fissures, burning more than itching, localized on the dorsal aspects and sites of fingers, sometimes extending to the dorsa of hands, with an anamnestic worsening after contact with water, detergents, etc.

Nummular eczema

A recurring nummular, papulo-vesicular, sometimes oozing dermatitis with some itching, localized on the dorsal aspects of hands and fingers, sometimes extending to the extensor aspects of extremities and back, occurring in bouts with some seasonal periodicity.

Atopic dermatitis

A continuous dermatitis, with dry, lichenified, slightly red infiltration, burning from fissures or itching, localized on the dorsal aspects of hands and fingers, preferably over the knuckles, worsening with certain seasons and when working with water. The patients have some personal history of atopic diseases and may, of course, have other signs of atopic dermatitis.

Pompholyx

A recurring itching eruption with deeply seated, fresh or inactive vesicles with some or no erythema, localized on the palms, volar aspects and sides of fingers, sometimes with similar lesions in the soles.

MATERIAL AND METHODS

Patients (I, II, III, VI)

Sixtysix female patients with patch test verified nickel allergy and hand eczema, who visited our out-patient department during 1971-1973 were invited to participate in a clinical investigation (I). Six years later all 66 patients were invited to a follow-up investigation and 63 accepted (II). To register the effect on dermatitis 17 patients with pompholyx type hand eczema (III + VI) were challenged with nickel sulfate per os and 11 patients were exposed externally with nickel-containing objects (III). Eight healthy volunteers (V) without nickel sensitivity ingested nickel sulfate and blood nickel concentration and urine nickel excretion were determined at different intervals after ingestion (V). Five patients with nickel sensitivity and pompholyx type hand eczema participated in a micromorphological study of orally challenged flare-up reactions (VI).

Clinical evaluation (I, II)

On the basis of a standardised questionnaire and clinical picture the hand eczema was classified according to given definitions. At the primary investigation (I) 55 patients were examined in person while the other 11 patients were classified on the basis of telephone interviews and earlier records. At the follow-up investigation (II) 55 patients were examined in person and eight patients were classified according to earlier investigation, records and a mailed questionnaire.

Internal nickel provocation (III, VI)

In a double-blind study (III) 12 patients ingested 5.6 mg nickel (25 mg $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) alternating with a lactose placebo capsule. Five patients were challenged orally with 5.6 mg nickel to study the micromorphology of flare-up reactions (VI).

External nickel provocation (III)

For 6 minutes 11 patients "washed" their hands in a bowl containing about a kilogram of different nickel-containing objects, such as coins, paperclips and keys. All objects were positive in the qualitative nickel test (Fisher 1973).

Registration of activation of dermatitis (III, VI)

At both internal and external nickel provocation the volar aspect of each hand was divided into 17 areas limited by the natural furrows, and the number of vesicles were counted before and after provocation. Both types of provocation were performed at a time of low eczematous activity. Five patients (VI) were admitted to the ward 4-7 weeks after epicutaneous and intracutaneous testing and challenged orally. For the following 24 hours the patients were repeatedly examined to register different types of flare-up reactions and finally, the histopathologic reactions were studied.

Patch testing (I, II, VI)

Patch testing, which - if positive - qualified the patients to participate in the study (I) was performed with a standard battery including 5% NiSO_4 in petrolatum and 1% CoCl in petrolatum (Trolle-Lassen, Copenhagen, Denmark) placed on Al-test units (Imeco, Astra Agency Co., Sweden). At retesting 7-9 years later (II, VI) the same NiSO_4 concentration was used (5%) but now placed in Finn Chambers (Pirilä 1975). Benzalkonium chloride 1-2% in aqueous solution in Finn Chambers was used to induce a toxic reaction (VI). All tests were applied 24-48 hours and read 72 hours after application. Test sites: upper back (I), upper left arm (II), buttock (VI).

Intracutaneous testing (VI)

Tuberculin 0.1 ml 2 TU (purified protein derivative, PPD, Statens Serum-institut, Copenhagen, Denmark) was injected intracutaneously on the right buttock and the reaction read after 72 hours.

Punch biopsies, fixation and staining (VI)

Punch biopsies, 2 mm diameter, for light microscopy and direct immunofluorescence were taken from marked 4-7 week old test areas and from the hypothenar region before and after oral challenge with nickel. The specimens for light microscopy were immediately fixed in 10% buffered formalin solution. After histotechnical preparations, the 3-4 μ thick sections were stained according to the following methods: haematoxylin-eosin, Giemsa, toluidine blue, McManus and Weigerts elastin stain.

Direct immunofluorescence

The specimens were quickly frozen or preserved in a transport medium described by Michel et al (1972) for a few hours before they were frozen in a mixture of propane-butane to the temperature of liquid nitrogen. Cryostat sections were incubated with fluorescein-labelled antisera from rabbit anti-human IgG, IgA, IgM, complement 3 and fibrinogen (purchased from DAKO Immuno-globulins Ltd., Copenhagen, Denmark) and examined according to the technique detailed by Beutner et al (1979).

Determination of serum IgE (II)

Serum IgE was determined according to the radioimmunoassay, Phadebas, IgE PRIST^(R) (Pharmacia, Uppsala, Sweden).

pH measurements (IV)

Distilled, deionized water was adjusted to pH 5.0, 3.5, 3.2 or 3.0 with hydrochloric acid (Merck p.a.) or to pH 11.0 with sodium hydroxide (Aristar, BDH). pH was measured with a pH meter pHM 26 C (Radiometer A/S, Copenhagen, Denmark).

Determination of nickel in water boiled in different types of saucepans (IV)

After chelating with 2 ml 2% ammonium pyrrolidine dithiocarbamate (BDH), the samples were extracted to an organic phase with 5 ml methylisobutylketone (BDH) and assayed by atomic absorption spectrophotometry (Perkin Elmer 303).

Determination of nickel in blood and urine (V)

All analyses were performed as direct determinations and no dilution of the samples, addition of matrix solvents, acids or other modifications of the samples were made. Thirty μ l blood, serum or urine were pipetted into graphite microboats and the samples were dried and preashed in a laboratory oven at 100°C resp. 600°C. After preashing the samples were analysed on an IL 550 (Instrumentation Laboratory Inc.) atomic absorption spectrophotometer equipped with an IL 555 graphite furnace during the run of a special temperature program (Christensen et al 1979).

Statistics

Statistical techniques included testing by Student's t-tests (IV, V), rank sum test (II, V), Fisher's exact test (II) and computations of correlation coefficient and linear regression analysis by the least-squares method (V).

RESULTS AND DISCUSSION

DIAGNOSIS AND HISTORY IN NICKEL SENSITIVE PATIENTS WITH HAND ECZEMA

Incidence of hand eczema in nickel sensitive patients (I)

Among 149 consecutive nickel sensitive patients diagnosed during January 1971 - September 1973 70 patients (47%) with hand eczema were found. This figure corresponds well to the incidences earlier reported (Bonnevie 1939, Fisher & Shapiro 1956, Wagmann 1959, Marcussen 1960, Wahlberg & Skog 1971, Cronin 1972, Peltonen 1979).

Type of hand eczema (I)

Among 66 nickel sensitive patients with hand eczema 51 (77%) were classified as having a pompholyx eczema, whereas the remaining 15 patients had a non-pompholyx type. (See Eczema definitions). This predominance of pompholyx in nickel sensitive patients has surprisingly not been reported in the earlier studies having about the same incidence of hand eczema in nickel sensitivity as in the present material. Fisher (1978) has questioned this proportion and almost denied the existence of pompholyx in connection with nickel sensitivity in U.S.A. Menné & Thorboe (1976), Kaaber et al (1978, 1979), Jordan & King (1979), Peltonen (1979), Kaaber (1980), Burrows et al (1981) have reported several patients with nickel allergy and pompholyx. After our primary study 1973 - 1974 we continue to see many new patients presenting with nickel sensitivity and the pompholyx type of hand eczema. The high proportion of patients found with pompholyx may be due to a selection mechanism. Because of their very active dermatitis these patients may seek specialist-care far more frequently than nickel sensitive patients with other types of hand eczema. It is none the less remarkable that the high proportion of pompholyx found in the present material is not reported in earlier studies.

Correlation between metal sensitivity and patch testing (I, II)

In 92 - 98% of the patients (I, II) a correlation between a history of metal sensitivity and patch test result was found, and this high figure of concordance agrees very well with the investigations of Peltonen (1979) and Prystowsky et al (1978), but not as well with the figure reported by Kiefer (1979) in an interview study. However, according to our experience it is very unusual that the history of metal sensitivity does not correlate to the patch test result in nickel allergy; in only a few patients does one remain uncertain regardless of the time and ambition invested on the patients' history.

Debut of metal sensitivity in relation to appearance of hand eczema (I)

The patients first noticed metal sensitivity at a mean age of 25 years, while the hand eczema appeared at a mean age of 32 years. Nearly the same ages for debut of metal sensitivity and hand eczema are reported by Cronin (1972) and Wahlberg & Skog (1971). In 73% of the patients the metal sensitivity started before the hand eczema, in 25% simultaneously and only one patient claimed that the hand eczema started before she noticed metal sensitivity. Marcussen (1960) reported that dermatitis of the hands was primary in 18% of nickel sensitive patients, while in 25% hand eczema occurred after sensitization elsewhere on the skin. On the other hand Marcussen (1960) concluded that 86% of the patients had been sensitized by nickel containing objects unconnected with their occupation. Cronin (1972) found that hand eczema appeared in 46% of 50 patients after the developing of nickel sensitivity and in 7 (14%) patients the hand eczema occurred first. Wahlberg & Skog (1971) reported that in 16 of 53 (30%) nickel sensitive patients the dermatitis started on the hands, whereas Wilson (1956) and Reichenberger et al (1976) reported that hand dermatitis in nickel sensitive patients was primary in 1 of 85 (6%) and in 38 of 198 (19%) cases, respectively. The figures in the present material indicate that primary sensitisation with nickel in the hands is rather uncommon. The fact that most of the patients had dermatitis localized to the volar aspects of hands, where stratum corneum is very thick and allergens thereby penetrate poorly, may be a factor contributing to the different proportions discussed here.

Occupation in relation to hand eczema (I, II)

In most of the patients the eczematous activity was not correlated to occupation, vacation, change of occupation or contact with nickel coated objects. No particular occupation predominated at the start of hand eczema. Most of the patients with pompholyx type hand eczema experienced bouts of eczema about once a month but not in relation to the menstruation cycle. Marcussen (1960) and Menné & Bachmann (1979) state that dermatitis in nickel sensitive patients in 40 - 60% starts on the hands in occupations with heavy nickel exposure, such as hairdressers, cashiers shop assistants, seamstresses, metal industry and restaurant workers. Wahlberg (1975) found 14 of 35 (40%) nickel sensitive patients among hairdressers with hand eczema, whereas Reichenberger et al (1976) stated that none of 37 nickel sensitive hairdressers had been sensitized in their occupation. Fregert (1975) found 19% of nickel sensitive patients with hand eczema occupied in cleaning work, but 11 other occupations were found in the remaining 81% of the patients. The figures reported by Marcussen (1960), Wahlberg (1975) and Menné & Bachmann (1979) were not found in the present material, in which 19 different occupations were stated at start of hand eczema and where occupations with heavy nickel exposure were rather uncommon. Probably the different proportions found depend to a certain extent on selection of material.

Secondary eruptions (I)

Secondary eruptions were found in 52% of the patients and all common sites as elbow flexures, eyelids and neck were equally represented, aside from 12 patients who had plantar eruptions. Calnan (1956), Marcussen (1957) and Waggmann (1959) reported secondary eruptions in about 75% of their nickel sensitive patients and showed that suspender dermatitis was especially associated with the occurrence of secondary eruptions, predominantly located in the elbow flexures. The lower frequency of secondary eruptions found may be due to the low incidence of suspender dermatitis in the present material compared to the incidence in the studies mentioned above.

Conclusion

The combination of nickel sensitivity and hand eczema as well as the opposite relation hand eczema and nickel sensitivity is common in an out-patient material. Pompholyx is common in female patients with nickel allergy and a history of metal sensitivity should be carefully enquired for when examining such a patient. In most patients nickel sensitivity is induced by nickel plated objects before the appearance of hand eczema and primary eruptions in the hands seem very unusual at present. Secondary eruptions are found in half of the patients with nickel sensitivity and hand eczema and the clinician should be familiar with this phenomenon, if it is not to be overlooked. The correlation between a history of metal sensitivity and the patch test result in nickel sensitive patients is so high that nickel could be excluded from the standard battery when testing a patient with a typical metal history.

PROGNOSIS AND UNFAVOURABLE FACTORS INFLUENCING THE PROGNOSIS IN NICKEL SENSITIVE PATIENTS WITH HAND ECZEMA

Prognosis (II)

By a follow-up study of 63 of the 66 female patients with nickel sensitivity and hand eczema 6 years later it was found that 30% had healed. However, only 18% of the patients with pompholyx compared to 77% of the patients with non-pompholyx were healed. Actually the majority of the patients with non-pompholyx had rather short periods of hand dermatitis with minor personal discomfort. Eczematous activity was reported unchanged and increased in 17 and 4 patients respectively, and decreased in 23 patients. This poor prognosis for nickel sensitive patients with pompholyx was in fact suggested in our primary study (I), where the patients had had symptoms for a mean of 9.3 years. Fregert (1975) found no healed among 29 nickel sensitive females with hand eczema in a 10 year follow-up of an occupational material. Thus the prognosis in nickel sensitive patients with hand eczema in a general clinical material was better than in an occupationally selected material, but it may greatly depend on the type of hand eczema.

Unfavourable prognostic factors (II)

1. Atopic disease

A personal and/or family history of atopic disease was found in 44% of the patients (50% in the pompholyx group compared to 23% in the non-pompholyx group). Oddoze & Témime (1968) reported a high frequency of atopy in patients with pompholyx eczema. The relationship between atopy and nickel allergy is discussed in several papers. Epstein (1956), Dobson (1963) and Watt & Bauman (1968) report a marked positive correlation between nickel allergy and atopy, whereas Calnan (1956), Wilson (1956), Marcussen (1957) and Caron (1964) found no such connection. The presence of hand eczema in these patients with nickel allergy was, however, not stated. The pathogenetic association between pompholyx-atopy-nickel allergy should be clarified, but until now no studies have been undertaken to objectively evaluate these connections. Patients with atopy were none the less found to have a more unfavourable prognosis than non-atopics among my patients with nickel allergy and hand eczema.

2. Concomitant cobalt allergy (I, II)

A co-existing nickel/cobalt sensitivity was found in 33% of the patients with hand eczema. Fregert & Rorsman (1966) and Cronin (1980) report figures of 37% and 29%, respectively, of co-existing nickel/cobalt allergy in path tested females; thus in this aspect patients with hand eczema do not differ from other nickel allergics. Menné & Bachman (1979) report that only a few cobalt sensitive subjects were found amount nickel sensitive patients in a prevalence study, which indicates that a co-existing nickel/cobalt allergy is higher in a clinical material. Menné & Bachmann (1979) therefore assume that a concomitant cobalt allergy may reflect an unfavourable prognosis. In the present material only 4 of 21 (19%) concomitant cobalt sensitive patients were healed compared to 15 of 42 (36%) patients without cobalt sensitivity. Even if no statistical significance was found this result seems to agree with Menné's & Bachmann's assumption (1979).

3. Immediate-type contact dermatitis (II)

A history of immediate type contact dermatitis to different types of food-stuffs was evident in 11 (17%) of the patients. All patients had pompholyx and none were healed. The patients denied any discomfort while handling food-stuffs prior to development of hand dermatitis. It was shown by Hjorth & Roed-Petersen (1976) and Krook (1975) that immediate-type reactions are more easily provoked in previously affected skin and this observation agrees with my patients' history.

4. Duration of nickel sensitivity (II)

By retesting 54 patients with NiSO_4 (5%) 7-9 years later, 2 patients were found negative. This low fall-out figure agrees with the figures reported by Fisher & Shapiro (1956) and Marcussen (1959b).

5. Determination of serum IgE (II)

Compared to a control material IgE was not found elevated in patients with nickel sensitivity and hand eczema. Determination of IgE was not found valuable in evaluating the degree of personal atopy or predicting the prognosis of hand eczema in the present material.

Conclusion

The duration of an acquired nickel sensitivity is at least one decade. Nickel sensitive patients with hand eczema of the pompholyx type have a significantly poorer prognosis than patients with non-pompholyx hand eczema. Among nickel sensitive patients 3 groups seem to stand out: Firstly a large group of patients with contact allergy and without hand eczema; secondly a group of patients with hand eczema of the non-pompholyx type, who seem to run a relatively short and mild course of hand dermatitis; thirdly a group of patients with pompholyx who have a chronic eczema causing much personal discomfort and disability.

Atopy is found frequently associated with nickel sensitivity and hand eczema and influences the prognosis significantly in a negative direction. Even associated factors as concomitant cobalt allergy and immediate-type contact

dermatitis are rather frequent in nickel sensitive patients with hand eczema and seem to influence the prognosis unfavourable. Examinations directed toward these 3 possible co-existing events should be undertaken in patients with nickel allergy and hand eczema. Determination of IgE was not found valuable in the present material.

CLINICAL REACTION AFTER INTERNAL AND EXTERNAL NICKEL PROVOCATION

1. Activation of hand eczema (III, VI)

Seventeen patients ingested 5.6 mg nickel and in 13 patients an aggravation based on subjective symptoms and by an increase of palmar vesicles was observed after 24-30 hours. The vesicles increased by a mean factor of 8. All positively reacting patients complained of palmar itching occurring an average of 10 hours after ingestion.

2. Maculo-papular rash (III, VI)

In 10 of the 17 orally exposed patients a maculo-papular rash was observed usually located over the abdomen, in the elbow flexures and around the neck. This eruption usually appeared after 3-5 hours and intensified during the next 20 hours. Most of the patients denied that they earlier had had dermatitis in these localizations.

3. Flare-up of earlier patch test and contact dermatitis reactions (III, VI)

In 12 of the 17 orally provoked patients a flare in old patch test sites or earlier contact eczema reactions was observed. About 4-10 hours after nickel ingestion the patients noticed itching and at 10 hours erythema and some infiltration could be observed. At 24 hours there was a strong eczematous reaction with erythema, infiltration, papules and/or vesicles on an area 2-3 times larger than the original patch or contact eczema reaction. Impressively, long intervals of 1 month - 10 years since the original dermatitis and reactivation by oral nickel ingestion have been observed or claimed by the patients.

4. Urticarial reactions (III)

In 2 patients urticarial reactions were observed 3-6 hours after nickel ingestion. In one of the patients oedematous swelling of the hands, wrists and eyelids and disseminated weals were seen together with a systemic reaction with a drop in blood pressure and rise of pulse rate. At an earlier provocation with 0.44 mg nickel the patient reacted with a few scattered weals. She had a 3-year history of pompholyx as well as urticarial bouts.

Reactions seen by other investigators after systemic administration of nickel

Kaaber et al (1978, 1979) reported an aggravation of hand dermatitis in 26 of 42 patients at a dose of 2.5 mg nickel; 2 other patients flared on 1.2 and 0.6 mg, respectively. They also reported urticaria-like eruption in 4 patients 2-6 hours after ingestion of nickel. Cronin et al (1980) found an exacerbation of hand eczema in 5 of 5, 3 of 5 and 2 of 5 patients on the

doses 2.5, 1.25 and 0.6 mg nickel, respectively. Cronin et al (1980) reported an erythema around the umbilicus, sides of neck, elbow flexures and anterior forearms 3-11 hours after ingestion of 0.6-2.5 mg nickel in 9 of 15 patients. Cronin et al (1980) also observed flare of the nickel patch test site, usually more intense than the original test reaction in 9 of 15 patients, provoked with the different doses (2.5, 1.25, 0.6 mg nickel).

Smeenk (1977) reported vesiculo-bullous eruptions on the hands, more or less generalized exanthems and flare-ups at the sites of earlier contact eczema in 7 nickel sensitive patients after intravenous infusion through metallic needles. Stoddard (1960) described generalized urticarial and eczematous reactions in 2 nickel sensitive patients, who also recieved infusions through nickel containing needles, and McKenzie & Aitken (1967) report a case with chronic urticaria related to the insertion of a nickel containing nail in the femoral neck. Kvorning (1975) reported red vesiculous skin lesions symmetrically on the lower part of the abdomen and on lateral aspects of thighs in 6 metal sensitive patients in connection with laparotomy where stainless steel retractors were claimed responsible. Rudzki & Grzywa (1977) reported a flare on the site of a previous nickel contact dermatitis in a Polish woman eating 250 mg margarine containing 50 µg nickel. Boonk & Ketel (1979) reported induction of a pompholyx like dermatitis and Lacroix et al (1979) described an urticarial vesiculous generalized eruption in a nickel sensitive patient after swallowing a nickel containing Dutch florin and a Canadian quarter, respectively. Holti (1974) reported the development of anaphylactoid reactions, urticaria and angio-oedema after intravenous infusions through nickel plated cannulae. Histologically the lesions showed vasculitis rather than eczema. Passive transfer of serum ad modum Prausnitz-Küstner was positive. Consequently, several reports show similar results as found in the present material.

In accordance with reactions observed after systemic administration of nickel Kaaber et al (1979) and Christensen & Kristensen (1981) have observed exacerbation of hand dermatitis as well as secondary eruptions in about 75% of the patients treated with a chelating drug (Disulfiram) 1-2 weeks after start of treatment. These exacerbations were seen at a time, when blood nickel concentration and urine nickel excretion were markedly elevated. Even 2 cases of leukocytoclastic vasculitis occurred during Disulfiram treatment (Kaaber et al 1979).

On the other hand two studies dealing with the question of activation of dermatitis by ingested nickel are reported with negative results. By feeding 10 nickel sensitive women with chronic vesicular hand dermatitis 0.5 mg nickel daily twice a week as a supplement to the regular diet, Jordan & King (1979) found that only one patient experienced deterioration of her hand dermatitis. They consider the dose of 0.5 mg within the physiological range of daily nickel intake, but the dose of 5.6 mg as unphysiological. Burrows et al (1981) gave 22 nickel sensitive patients with palmar dermatitis initially 2 mg and later 4 mg nickel daily on 2 following days during 2 weeks and lactose as placebo in a double-blind study. Based on the patients' and doctor's opinion they found no significant differences between placebo and nickel, and conclude that there is no connection between the amount of nickel encountered in an ordinary diet and exacerbation of dermatitis.

Several factors influence the amount of nickel ingested and absorbed (see later), therefore this amount can vary greatly and occasionally reach high amounts (Dencker et al 1971, Ellen et al 1978, Brun 1979), which can activate dermatitis in nickel sensitive patients. On the other hand it is not solely a question of dose. The individual sensitivity, probably reflecting the immunological state of the patient, assessed from no activation in some

patients to vigorous generalized eczematous toxicoderma-like reactions in others, is apparently of importance. The finding by Cronin et al (1980), that some patients are not activated in their dermatitis, although they absorb nickel, supports the idea that individual sensitivity is an important factor.

External provocation (III)

When the patients for 6 minutes "washed" their hands in nickel 3 of 11 patients complained of itching but no eczematous changes were observed. Case reports of hand eczema located in the palms and induced by nickel containing coins are reported by Bettly (1971) and Husain (1977) and it can always be discussed if 6 minutes of intensive handling imitate real conditions. Band Pedersen et al (1974) however claim that handling coins for 5 minutes gave the same degree of contamination as 4 hours regular handling.

Conclusion

Nickel given orally can activate hand eczema of pompholyx type in nickel sensitive patients along with other manifestations such as flare-up reactions of earlier patch test sites and contact dermatitis, maculo-papular rashes and urticaria-like eruptions in about 75% of challenged patients. Therefore the principle "endogenous contact eczema" seems sufficiently documented in this type of patients. The degree of activation is, besides the dose dependent on the patients' individual sensitivity. External provocation with nickel hardly activates pompholyx. Pompholyx should be considered a secondary eruption in nickel sensitive patients. These observations are in accordance with most of the patients' histories with bouts of eczema independent of direct nickel-to-hand contact. Accordingly, information given to pompholyx patients by dermatologists as well as insurance policies should take this observation into account. Secondary eruptions as previously noted may be induced by oral nickel ingestion or by nickel administered systemically in other ways.

RELEASE OF NICKEL FROM STAINLESS STEEL UTENSILS (IV)

By boiling distilled deionized water at different pH (5.0, 3.5, 3.2, 3.0, 11.0) in new and used saucepans made of stainless steel (chrome/nickel 18/8) nickel was released in amounts from 0.2 to 38 ug. No nickel was released at neutral or alkaline pH. The amount of nickel released was correlated to a decrease in pH. No nickel was released from saucepans made of aluminium, aluminium coated with teflon, or enamel. Brun (1979) boiled acidic foods for 1 hour in stainless steel (10/18 Ni/Cr) saucepans and found that nickel was released in amounts as high as 1.5 mg. He showed that oxalic acid, naturally present in acidic foods, was responsible for this high release of nickel. The release of nickel is obviously much higher when more natural conditions as boiling of foods is performed compared to the more arteficial conditions of boiling acidified water. Ellen et al (1978) report that coffee made in a stainless steel coffee machine contained 0.13 mg Ni/l, whereas coffee brewed in a plastic percolator only contained 0.01 mg Ni/l. Red currant juice made in a domestic juice centrifuge contained 5.6 mg Ni/l, whereas strawberry juice made in the same apparatus contained less than 0.1 mg Ni/l. Probably the metal area exposed, time of contact, agitation, pH levels and chemical and physical properties of stainless steel are factors of importance, when comparing the results obtained in the studies referred to.

Conclusion

Varying amounts of nickel can be released by preparing acidic food-stuffs in stainless steel utensils and the nickel amount released may reach levels, which - as shown above - can activate the dermatitis in nickel sensitive patients with pompholyx type eczema. Therefore the use of stainless steel utensils should be avoided by these patients. The degree of nickel contamination by industrial preparation, storing and canning has unfortunately not been investigated in detail.

NICKEL IN FOOD

Amount of nickel in food

The amount of nickel in different types of food-stuffs has been studied and reviewed by several investigators (Schroeder et al 1962, Dencker et al 1971, Schlettwein-Gsell & Mommsen-Straub 1973, Kirkpatrick & Coffin 1974, Thomas et al 1974, Ellen et al 1978, Myron et al 1978, Brun 1979). Different amounts varying from 0.2 - 4.5 mg in total daily diets are reported as well as great variations in different food-stuffs. Fregert (1971) and Ellen et al (1978) report nickel amounts of 0.25 - 1.3 mg/l in the first water tapped in the morning and McNeely et al (1972) found 0.2 mg Ni/l in tap water in Sudbury, Ontario.

Factors influencing the amount of nickel ingested and absorbed

Nickel is ubiquitous in nature and several factors influence the amount ingested and absorbed.

1. Differences in concentrations and physico-chemical structure in the parent soil (Robinson & Edgington 1935, Mitchell 1971, Christensen 1979).
2. Spreading of sewage sludge and municipal composts, impurities in certain agricultural chemicals and fertilizers and industrial pollution (Barrows 1966, Le Riche 1968, Lagerwerff et al 1970, Purves 1972).
3. The ability among different plant species to absorb trace metals (Greer et al 1952, Brown 1961, Van der Merve & Perold 1967).
4. Soil pH, in that lowering pH increases uptake (Mitchell 1971, Quaterman 1973).
5. Manufacturing processes as harvesting, cooking and canning (Drinker et al 1924, Thomas et al 1974, Christensen & Möller 1978, Ellen et al 1978, Brun 1979).
6. Absorption, calculated to 5-10% of the ingested amount (Horak & Sunderman 1973, Nodiya 1972) depends on structure and binding of nickel (Tiffin 1971) and the presence of chelating compounds (Vohra et al 1963) or compounds facilitating absorption (Spruit 1979).

In general vegetables and fruits such as asparagus, beans, mushrooms, onions, corn, spinach, tomatoes, peas, pears and rhubarb contain relatively high amounts of nickel. High amounts are also reported in herring, oysters, chocolate, nuts, tea and cocoa. In general small amounts of nickel are found in meat and milk products.

Discussion and conclusion

The study of Kaaber et al (1978) indicates that a low nickel diet reduces the hand eczema activity in nickel sensitive patients. Many factors, most of them impossible to control influence the amount of nickel ingested and absorbed. Therefore, from a practical point of view it is very difficult to accomplish a diet with low contents of nickel and such attempts are not recommended. The following efforts to reduce nickel ingestion in nickel sensitive patients with hand eczema of the pompholyx type are recommended:

1. Don't be a vegetarian.
2. Avoid cocoa, tea, chocolate and nuts.
3. Don't prepare acidic food-stuffs in stainless steel utensils.
4. Let the tap water run 30 sec. - 1 minute after a long period of shutting off.

NICKEL CONCENTRATION IN BLOOD AND URINE IN CONNECTION WITH NICKEL INGESTION (V)

By following blood nickel concentrations in close intervals after ingestion of 5.6 mg nickel the maximal concentration was found 2.5 hours after ingestion and in average the nickel concentration in serum was increased 21 times. Cronin et al (1980) also found that the peak concentration of serum nickel occurred 2.5 hours after oral nickel challenge. Great variations in blood nickel concentration were found both in the present study and in the study of Cronin et al (1980). Maximal excretion of nickel in the urine was found within the first 8 hours after challenge and in average the nickel excretion increased 65 times (V). However, 40-48 hours after ingestion nickel urinary excretion was still significantly elevated compared to the excretion before nickel ingestion. The urinary excretion of nickel was found to be closely positively correlated to serum nickel concentration and the half-life in serum was 11 hours. Menné et al (1978) and Cronin et al (1980) have also studied urinary excretion after oral ingestion and both groups observed great individual variations. Cronin et al (1980) conclude that the severity of the dermatitis response parallels the size of the challenge dose but they do not correlate the severity of response to the nickel levels found in serum and urine. Absence of dermatitis response, however, was not correlated to absence of absorption (Cronin et al 1980).

Conclusion

An orally ingested soluble nickel salt is rapidly absorbed, but with great inter-individual variation. Maximal concentration in blood is attained 2.5 hours after ingestion. Absorbed nickel is quickly excreted in the urine proportionally to serum nickel concentration. Nickel excretion in urine seems to be the most reliable parameter to follow in connection with oral nickel ingestion and probably a single urine sample 5-10 hours after ingestion is sufficient to register this type of exposure.

MICROMORPHOLOGY AND SPECIFICITY OF PATCH TEST AND HAND ECZEMA FLARE-UP REACTIONS (VI)

Five nickel sensitive patients with pompholyx ingested 5.6 mg nickel 4-7 weeks after patch testing with 5% NiSO₄ and 1-2% benzalkonium chloride, and intradermal testing with tuberculin. By that time all test reactions had subsided, but in all patients the nickel patch test sites flared with

erythema, infiltration, papules and vesicles along with flares on earlier contact dermatitis localizations. A time interval of 4 weeks - 4 years in this study between patch testing or earlier contact dermatitis reactions and reactivation by oral challenge was observed by us or claimed by the patients. The flare-up reactions were more intense and usually 2-3 times larger than the original patch test reaction. No flare-up reactions were observed corresponding to the benzalkonium or tuberculin test sites. Four patients reacted with an increased number of vesicles in their palms. Light microscopical examination of the flare-up reactions in nickel patch test sites and in the palms showed marked histopathological changes with dermal oedema, lymphocytic perivascular infiltration, spongiosis and vesicles. No or only slight inflammatory reaction was observed in the benzalkonium or tuberculin test sites and no changes comparing pre- and postprovocational biopsies were observed in these test sites. Direct immunofluorescence examination did not reveal any significant findings of IgG, IgA, IgM, complement 3 or fibrinogen comparing specimens taken before and after provocation. Other clinical reaction such as a maculo-papular rash were observed but not examined histologically.

Conclusion

Flare-up reactions of earlier nickel patch test sites or contact dermatitis reactions can be induced after month - years when the antigen is ingested. Usually the flare-up reactions are more intense than the original patch test reaction. Flare-up reactions in nickel allergics seem to be specific. The observed flare-up reactions in both nickel patch test sites and palms are eczematous and correspond in that aspect with the light microscopical findings. Induction of flare-up reactions in nickel sensitive patients may serve as a model for more detailed investigation of pathoimmunological events taking place in delayed hypersensitivity in human beings.

TREATMENT OF NICKEL SENSITIVE PATIENTS WITH HAND ECZEMA

Nickel allergy is very common and in cases with hand eczema a disabling condition for many patients. Attempts to reduce sensitisation rate are seriously needed. From the point of view that nickel allergy is predominantly induced by nickel containing objects in clothing and nickel-plated trinkets it seems meaningful to reduce the sensitisation possibility from these items. Probably legal regulations would facilitate elimination of such risk items.

When a hand eczema of the pompholyx type is established one must attack the problem along several therapeutical lines. It is advisable to reduce the oral intake of nickel in accordance with the recommendation described earlier. For flares of pompholyx we have experienced some beneficial effect from corticosteroid depot preparations injected intramuscularly, whereas long term use of topical corticosteroids has a more dubious effect in this condition (II). Recently it has been reported that the chelating drug (Disulfiram) has a good therapeutic effect in nickel pompholyx (Kaaber et al 1979, Kaaber 1980). We have the same experience after treating 11 patients with Disulfiram 200 mg daily for 8 weeks (Christensen & Kristensen 1981). In nickel sensitive patients with chronic pompholyx treatment with Disulfiram appears to be the most promising therapy today. Unfortunately, liver damage has been observed (Kaaber et al 1979, Kristensen 1981) so that liver tests should be performed during this treatment. Finally, if the patients have an immediate type contact dermatitis or a traumatic and obviously nickel contaminated occupation they should be transferred to other non-traumatic and non-sensitising occupations.

GENERAL SUMMARY

The prevalence of nickel allergy in females is today about 10%. Half of the patients with nickel allergy in a dermatological department have hand eczema and most of these patients suffer from a chronic vesicular palmar eruption of the pompholyx type. The history and clinical picture are mostly in accordance with an endogenous eczema and ingested nickel activates the hand dermatitis, whereas external contact with nickel hardly provoke any dermatitis. Occasionally high amounts of nickel in the diet may be responsible for the periodic bouts of hand eczema.

The prognosis in nickel sensitive patients with pompholyx is very bad and associated factors as atopy, concomitant cobalt allergy and immetiate-type contact dermatitis are coexisting rather frequently and seem to influence the prognosis unfavourably.

Secondary eruptions as maculo-papular rashes usually located in the elbow flexures and sides of neck occur in half of the patients sensitive to nickel. In connection with oral provocation such secondary eruptions are observed along with flare-up reactions of earlier nickel patch test sites and contact dermatitis reactions. Clinically and morphologically flare-up reactions of nickel patch test sites as well as hand eczema flares are eczematous and hand eczema of the pompholyx type should be considered a secondary eruption.

An ingested soluble nickel salt is rapidly absorbed and after 2.5 hours a maximal concentration in blood is achieved. Absorbed nickel is excreted in the urine corresponding to a fall in blood nickel concentration and maximal excretion is found within 8 hours after ingestion. The urinary excretion of nickel seems to be the most reliable parameter to register in connection with oral nickel challenge.

Today nickel sensitivity among females is very common and seems to increase. In accordance with the risks combined with nickel allergy it is highly warranted to reduce sensitising exposure. Probably legislation efforts are needed to limit the widespread use of nickel-plated objects in clothings and jewellery. In patients with nickel sensitivity and chronic pompholyx, treatment with nickel chelating drugs seems promising and further investigations along this therapeutic line are warranted.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to

Professor Halvor Möller, my superior, teacher and friend, who initiated this work, for his very generous and enthusiastic guidance and invaluable continuous support throughout the investigation, to

Assistant Professor Holger Hansson and my colleague Bo Ljunggren for constructive criticism, to

Mrs Katarina Oxelbeck for very generous assistance in the secretarial work, to

Mrs Karin Lundberg for skilful technical assistance, to

Mr Björn Edman for fruitful statistical discussion, and to

Miss Joyce Carlsson for revising the English text.

Financial support was gratefully received from Svenska Livförsäkringsbolags Nämnd för Medicinsk Forskning and The Swedish Work Environment Fund, Stockholm, Sweden.

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Nickel allergy and hand eczema

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A clinical study was performed in 66 female patients with hand eczema and contact allergy to nickel. They were drawn from a basic material of 165 patients with nickel allergy in which hand eczema occurred in 86 cases (52 %). The hand eczema started at an average age of 32 years and it had been preceded by a metal hypersensitivity for an average of 6 years. The eczema was found to be chronic with a mean duration up to the time of examination of 8 years. It was associated with secondary eruptions in half of the cases. The hand eczema showed a low degree of relevance with regard to dependance of occupation or vacation, as well as to exacerbation of the dermatitis after a direct contact with nickel-coated objects. The clinical examination disclosed in 77 % a pompholyx, *i.e.* a symmetric vesicular eruption mainly located on the palms and volar aspects of fingers, and sides of fingers. The eczema often showed a periodic activity, with about 15 annual eruptions in the pompholyx cases. It is concluded that simple external contact with the metal can hardly explain the most common clinical pattern of the hand eczema in nickel allergy.

Key words: contact allergy – nickel – hand eczema.

Received for publication September 30, 1974

Eczematous contact allergy to nickel is very common, in recent statistics varying between 7 and 13 % positive reactions among epicutaneously tested patients (Fregert et al. 1969, Baer et al. 1973, North American Contact Dermatitis Group 1973). In our own department the equivalent figures of 8.9, 8.5 and 10.0 % have been registered for the years 1971, 1972 and 1973, respectively. As is regularly noted, the female to male preponderance was high; for those very years it was 13/1. In many cases, contact allergy to nickel is easy to diagnose on the basis of history and/or clinical findings, *viz.* when the location of the dermatitis is restricted to sites of direct metal contact. Then the positive patch test to nickel salt just implies a verification. In other cases, however, the positive nickel test is an unexpected finding when studying a patient with unclassified eczema (Cronin

1972). This is particularly the case in women with hand eczema.

Contact allergy to nickel is demonstrated in patients with hand eczema in 8–11 %; in females 12–21 %, and in males 0–2 % (Agrup 1969, Cronin 1972). Thus, female patients with hand eczema and nickel allergy constitute a considerable dermatologic problem, not least as the chronicity of the disease is impressive (Fregert 1974). A study was therefore performed in order to furnish a clinical description which was previously lacking.

Material and Methods

The basic material consisted of 182 patients with a contact allergy to nickel, 165 females and 17 males, demonstrated by epicutaneous testing during the time period January 1971 to September 1973, *i.e.* 32 months. From

this group, patients with hand eczema (86 females and 10 males) were selected for the clinical examination. With the purpose in mind of describing the hand eczema in nickel allergy, the 3 male patients, as well as males and females (7 and 16, resp.) with a concomitant other allergy, were excluded. However, simultaneously occurring cobalt allergy, found in 23 cases, was accepted. The remaining cases, comprising 70 female patients with nickel allergy and hand eczema, were invited to a clinical follow-up examination. In these 70 patients the dermatitis could be assessed in 66 cases, viz. in 55 patients appearing personally, in 7 patients who could be reached on the telephone, and in another 4 patients evaluated on the basis of records only.

At the clinical examination the patients were questioned about the duration of hand eczema and of metal sensitivity, respectively; the occurrence of dermatitis in regions except the hands ("secondary eruptions"); a history of atopic diseases; a problem of palmar hyperhidrosis; the usual localization of the hand eczema; the annual frequency of eczematous activity; a possible influence of work or vacation, of seasons, menstrual cycle and different food stuffs; and worsening of hand eczema provoked by direct contact with a nickel object. At the examination a present dermatitis was registered with regard to a detailed localization and to the type of lesions.

On the basis of history and the clinical picture, the hand eczema was finally classified according to one or more of the following five diagnoses:

Contact dermatitis type A ("Allergic contact eczema"). A recurring itching dermatitis with red papules and/or vesicles, localized on the dorsal aspects of hands and fingers, and the sides of fingers, sometimes extending to wrists and arms.

Contact dermatitis type B ("irritant dermatitis"). A more continuous dermatitis, reddish and scaling, often with painful fissures, burning more than itching, localized on the dorsal aspects and sides of fingers, sometimes extending to dorsa of hands, with an anamnestic worsening after contact with water, detergents, etc.

Nummular eczema. A recurring nummular, papulo-vesicular, sometimes oozing dermatitis with some itching, localized on the dorsal aspects of hands and fingers, sometimes extending to extensor aspects of extremities and back, occurring in bouts with some seasonal periodicity.

Atopic dermatitis. A continuous dermatitis, with dry, lichenified, slightly red infiltration, burning from fissures or itching, localized on the dorsal aspects of hands and fingers, preferably over the knuckles, worsening with certain seasons and when working with water. The patients have some personal history of atopic diseases and may, of course, have other signs of atopic dermatitis.

Pompholyx. A recurring itching eruption with deeply seated, fresh or inactive vesicles with some or no erythema, localized on the palms, volar aspects and sides of fingers, sometimes with similar lesions in the soles.

From this arbitrary and descriptive classification it appears that the sides of fingers are cross-roads for different types of eczema. Accordingly, some patients obtained more than one diagnosis.

Results

The clinical examination of 66 female patients with hand eczema and nickel allergy showed that 51, or 77.2 %, had an eczema of the pompholyx type (Table 1). Of these, 41 had pompholyx only, while the other

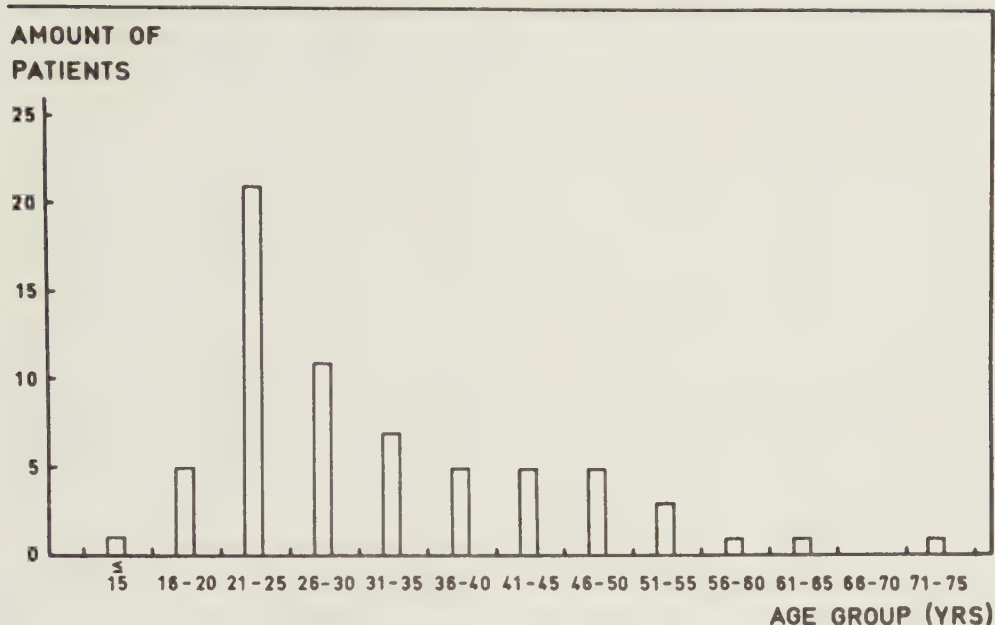


Fig. 1. Age of onset of hand eczema in 66 patients with nickel allergy.

10 patients had one additional diagnosis. On the whole, 13 of the 66 patients were classified with more than one diagnosis. Because of this preponderance of pompholyx in the material, the further presentation of data will concentrate on that group versus other eczema types.

The patients had noticed hypersensitivity to metals (ear-rings, brassière clips, bracelets, zips, suspenders, etc.) at a mean age of about 25 years. This holds true for all eczema groups (Table 2). Five patients denied a history of skin reactions to metals. Most cases of hand eczema started in the age group 21-25 years (Fig. 1) but the mean age for the whole material occurred at 32 years (Table 2). Thus, there was a mean interval of 5.9 years from the start of metal sensitivity to that of hand eczema. The metal sensitivity and the hand eczema had started simultaneously in 15 patients, and one patient did not notice metal sensitivity

until after the start of hand eczema. The duration of hand eczema up to the time of examination in the total material showed a mean of 7.9 years; this was, however, 9.3 years in the pompholyx cases but only 3.0 years in the non-pompholyx types.

A history of itching and/or dermatitis at sites where a direct metal contact could not be traced occurred in 34 of the 66 patients, *i.e.* in 51.6 % (Table 3). Such secondary eruptions were mainly located in elbow flexures, neck, eyelids and soles. The loca-

Table 1. Diagnoses made in 66 patients with nickel allergy and hand eczema

Contact dermatitis type A ("Allergic contact eczema")	9
Contact dermatitis type B ("Irritant dermatitis")	11
Nummular eczema	5
Atopic dermatitis	3
Pompholyx	51

Table 2. Hand eczema in nickel allergy. Age of onset of metal sensitivity and of hand eczema, the time interval in-between, and the duration up to the time of examination

Diagnosis	Age of onset of metal sensitivity			Age of onset of hand eczema			Time interval			Duration of hand eczema		
	n	mean	range	n	mean	range	n	mean	range	n	mean	range
Pompholyx only	39	25.1	6-54	41	32.0	15-72	39	6.4	0-30	41	8.3	1-40
Pompholyx + other eczema group(s)	9	25.8	8-43	10	28.6	15-45	9	2.4	0-8	10	13.6	2-60
All pompholyx patients	48	25.2	6-54	51	31.4	17-54	48	5.8	0-30	51	9.3	1-60
Non-pompholyx eczema	13	25.1	12-54	15	35.5	20-72	13	6.5	0-19	15	3.0	0-15
Total material of hand eczema	61	25.2	6-54	66	32.0	15-72	61	5.9	0-30	66	7.9	0-60

tion to eyelids and soles was particularly common in the pompholyx patients. Among the 11 pompholyx patients with involvement of the soles, six had a symmetric vesicular eruption, four had itching only, and one a keratotic, rhagadiform eczema.

The localization of eczematous lesions, according to history and clinical findings, is given in Table 4. As may be seen from the table, the eczema was symmetric in the large majority of cases. The distribution of lesions is also presented for the 41 patients of pure pompholyx because of the predominance of that group (Table 1). According to our definition, the dorsa of hands were not affected in any case, and the dorsa of fingers only periungually. The eczema involved the thenar, hypothenar and the distal areas of the palms particularly, as well as the volar aspects of the fingers, including the finger pulps. Since some of the patients lacked lesions at the time of examination, the figures presented under "Findings" are lower than those under "History". The characteristic localization of the nickel hand eczema has been schematically compiled in Fig. 2.

The eczematous activity varied greatly in the material, some patients having a more or less continuous problem, others experiencing a periodic activity. A recurring eruption was characteristic of the pure pompholyx group: 35 out of 41 patients had a mean frequency of 15.5 bouts per year (range 1/2 - 50).

The following information was obtained from 62 of the 66 patients with hand eczema: 29 patients reported deterioration of their eczema as an occupational consequence, or improvement during vacations. On the other hand, the remaining 33 patients endured eczematous activity quite independently of such changes in their every-day life. Only 16 patients had noticed an induction of their eczema in sites corresponding to possible nickel-coated objects.

Table 3. Secondary eruptions occurring in 34 of 66 patients (51.6 %) with nickel allergy and hand eczema

	n	Elbow flexures	Neck	Eyelids	Soles	Other locations
Pompholyx only	22	5	2	9	10	6
Pompholyx + other eczema group(s)	6	3	3	3	1	3
All pompholyx patients	28	8	5	12	11	9
Non-pompholyx eczema	6	1	2	1	1	2
Total material of hand eczema	34	9	7	13	12	11

A seasonal variation was reported by 30 patients, however, without any particular pattern. Palmar hyperhidrosis was a problem

for 15 patients, all in the pompholyx group. Only 3 patients had observed an increased eczematous activity in connection with their monthly periods. A variety of foods was held responsible for exacerbations in 10 cases.

A personal history of atopic dermatitis, bronchial asthma, or allergic rhinitis was obtained in 7 of 66 patients.

Discussion

Hand eczema is a common finding in patients with contact allergy to nickel, figures of 16–60 % having been reported in females (Calnan 1956, Wagmann 1959, Wilson 1956, Cronin 1972). In the present material 47% of the female patients with nickel and cobalt allergy had hand eczema (52 % if patients with concomitant other allergy are included). The mean age at start of hand eczema, 32 years, was exactly the same as that observed by Wahlberg & Skog (1971). A preceding sensitivity to metals had been noted by 46/62 patients, and the interval before development of hand eczema ranged from 0–30 years (Table 2). Cronin (1972) has observed a similar interval of 6 months to 40 years between the positive nickel test and the hand dermatitis in 23/50 women. It is impossible from these figures to conclude in what frequency a regular nickel dermatitis at the sites of earrings, suspenders, etc. progresses to a hand

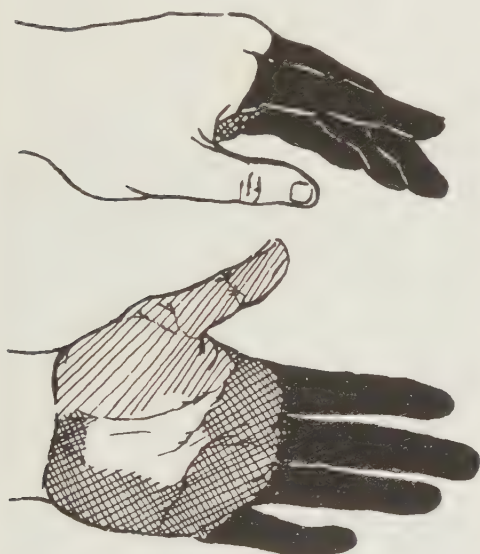
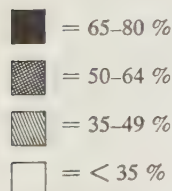


Fig. 2. Eczematous lesions in the 41 cases with nickel hand eczema of the pompholyx type. The distribution was obtained by compiling figures in Table 4 and thus illustrated:



(Drawing by S. Börsting)

Table 4. Localization of lesions in 66 patients with nickel allergy and hand eczema

	Total material of hand eczema (n=66)				Pompholyx only (n=41)			
	History		Findings		History		Findings	
	n	%	n	%	n	%	n	%
Symmetry	59	89	42	64	38	93	27	66
Dorsa of hands	14	21	8	12	0	0	0	0
Dorsa of fingers	23	35	11	17	7*	17	2*	5
Sides of fingers	51	77	35	53	35	85	27	66
Thenar	26	39	14	21	21	51	11	27
Hypothenar	32	48	19	29	27	66	16	39
Central palm	13	19	10	15	12	29	8	20
Distal palm	33	50	25	38	28	68	20	49
Volar aspects of fingers	36	55	30	45	31	76	25	61
Finger pulps	41	62	32	48	30	73	25	61

* Periungually only.

eczema without performing a retrospective or prospective study. This development occurs, however, so frequently that it constitutes a major problem among females with hand eczema.

The clinical picture in the present material showed a predominance (Tables 1 and 4) of a symmetric, vesicular, slightly inflammatory eruption with a predilection to the centrifugal areas of the palms, and to the sides and volar aspects of the fingers (Fig. 2). This type of hand dermatitis which is generally called pompholyx, acrovesiculatio recidivans, or dyshidrotic eczema, has not been demonstrated before in any material of patients with nickel allergy. We do not postulate that pompholyx implies the presence of nickel allergy; it may be considered a reaction pattern induced by several causes. The suspicion of contact allergy to nickel should, however, be raised when dealing with pompholyx in younger women. It is interesting that an equivalent development to pompholyx has been registered in many cases of chromate hypersensitivity in men (Reichenberger 1972).

The chronicity of the hand eczema in

nickel allergy is notorious. The mean duration until examination was 7.9 years (8.3 years in the patients with pompholyx only). Fregert (1974), in a 10-year follow-up of female patients with occupational hand eczema and nickel allergy, found that about 50 % had periodic symptoms, about 50 % continuous symptoms, and none was healed. This grave prognosis thus corroborates our findings with reference both to total duration of the eczema and to the impressive mean frequency of 15.5 annual exacerbations.

Calnan (1956), and later Wagmann (1959), differentiated between primary and secondary eruptions in nickel allergy. Secondary eruptions were found in 74 and 77%, respectively. The equivalent figure in the present material, selected with regard to hand eczema, was 55 %. The sites were similar to those mentioned by the earlier authors. It is, however, noteworthy that in our cases the soles were involved in 12/66 patients (10/41 patients with pompholyx only).

The relevance of positive patch tests to nickel is generally considered high. In the

European study nickel allergy was found responsible for the dermatitis in 64 % of patients with a positive nickel test (Fregert et al. 1969). In a hand eczema generally considered to have been elicited through contact allergy it is remarkable that more than half of our patients were troubled by eruptions regardless of occupation and vacation. Furthermore, 46 out of 62 patients denied any worsening of their hand dermatitis after direct contact with a particular metal object, although the usual reaction pattern at sites of intimate metal contact (ear-rings etc.) could easily be produced. All patients had earlier obtained detailed instructions on how to avoid contact with nickel and many of them had thoroughly transformed their milieu with this in mind. The effect of this, however, was poor or none.

Several further findings in the present material agree only to a small extent with the concept of the hand eczema in these women being solely elicited by external exposure to nickel. Among these may be mentioned the often complete symmetry; the lack of involvement of the dorsal aspects of hands and fingers in the pompholyx cases; the patients with an intense and daily contact with nickel, such as that of a cashier, but with a periodic instead of continuous eczema; one-sided eruptions in spite of exposure to both hands or to the other hand; simultaneous eruptions in hands and feet.

As a conclusion of our findings it appears quite possible that the recurrent pompholyx so common in nickel allergy may be elicited by a mechanism other than external exposure to the metal. In other words, the hands should be considered a secondary rather than a primary site.

Since regular food stuffs contain appreciable amounts of nickel (Wagmann 1959, Dencker et al. 1971) it is possible that the hand eczema is maintained by ingestion

of the metal in small amounts. As a consequence, an investigation of these patients with external and internal nickel provocation will be carried out and separately reported.

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PROGNOSIS IN NICKEL ALLERGY AND HAND ECZEMA

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ABSTRACT

A material of 63 female patients with nickel allergy and hand eczema was reinvestigated after 6 years. Thirty per cent of the patients were healed. Patients with the pompholyx type eczema had the worst prognosis. Start of hand eczema was not correlated to any particular occupation. There was a good correlation between a history of metal sensitivity and a positive patch test reaction. High frequencies of personal and family atopy were found and atopy influenced the prognosis to the worse. Determination of serum IgE was not found to be of any use in predicting the prognosis in patients with nickel allergy and hand eczema.

Key words: contact allergy - nickel - hand eczema - prognosis

INTRODUCTION

In an earlier study (Christensen & Möller 1975) the history and clinical picture in patients with nickel allergy and hand eczema were described. Pompholyx was found to be the predominant type of hand eczema. It has been shown that the prognosis in nickel-allergic patients with hand eczema is bad (Fregert 1975). To establish the prognosis in a clinically defined material with nickel allergy and hand eczema, our original material was reinvestigated. Also, since the duration of a once acquired delayed hypersensitivity is assumed to be almost life lasting,

the patients were retested with nickel.

The correlation between atopy and nickel allergy has been discussed in several papers (Calnan 1956, Epstein 1956, Wilson 1956, Marcussen 1957, Dobson 1963, Caron 1964, Watt & Bauman 1968, Forsbeck 1971, Wahlberg & Skog 1971). Some papers show a connection between nickel allergy and atopy, others do not. Clinical experience often indicates a relationship between pompholyx and atopy which actually has been postulated by Oddo & Témime (1968). High levels of serum IgE is correlated to atopic diseases (Johnsson 1976). In order to check these connections the patients were questioned on atopic history and their serum IgE was determined.

MATERIAL AND METHODS

In the original clinical study carried out in 1973-74 on 66 female patients with nickel allergy and hand eczema, 41 were classified as having pompholyx only, 10 pompholyx with an additional diagnose and 15 patients a non-pompholyx eczema (Christensen & Möller 1975) (the terms additional diagnose and non-pompholyx eczema contain the diagnoses contact allergic, irritant, nummular, atopic - eczemas). All 66 patients were now invited to a clinical follow-up which took place after about 6 years during winter 1980. In the group "pompholyx only" 37 patients appeared personally and 3 patients could be assessed by a questionnaire. Eight of 10 patients with "pompholyx + other eczema" showed up for the examination and 2 patients answered the questionnaire. In the remaining "non-pompholyx group" 10 of 15 patients appeared personally and 3 patients answered the

questionnaire. In all 55 of the 66 patients were seen personally, 8 patients answered the questionnaire and only 3 patients were impossible to retrieve (Table 1). The questionnaire contained the same standardized questions that were asked the patients examined personally.

1. At the clinical examination the type of hand eczema was classified on the basis of clinical picture and history according to earlier definitions (Christensen & Möller 1975). Eczematous activity as compared to the previous examination was classified as decreased, unchanged or increased (only the patients' own estimation was noted). The hand eczema was considered healed when no dermatitis had been present for the last 2 years.

2. Occupation during début of hand eczema as well as eczematous activity in connection with change of profession were noted.

3. The patients were requestioned about metal sensitivity and a history of immediate type contact dermatitis to different food-stuffs was noted. Epicutaneous retesting with 5% NiSO_4 in petrolatum was performed with Finn chambers (Pirilä 1975) during 48 hours and read after a further 24 hours. The same concentration of NiSO_4 (5%) was used in the original patch test 7 - 9 years earlier, but Al test was used instead of Finn chambers.

4. A history of personal and family atopic disease was asked for. Patients with present or earlier atopic disease (atopic eczema, allergic rhinitis, bronchial asthma) were classified as personal atopics, whereas family atopic disease was diagnosed when diseases as above were present in at least one of the parents or siblings. A venous sample for serum IgE was drawn and analyzed (PRIST^R, Pharmacia, Uppsala, Sweden).

5. The patients' experience of the therapeutical effect of topical corticosteroids was noted.

Statistical techniques included computations according to the rank sum test and the Fischer's exact test. Differences were considered not significant when p values were > 0.05 .

RESULTS

Clinical examination and eczematous activity

The result of the examination of 63 females with nickel allergy and hand eczema is shown in Table 1. In the group "All pompholyx patients" comprising 50 patients, 36 patients (72%) still had pompholyx, while 5 patients (10%) had got rid of their recurrent vesicular eruptions and instead had a non-pompholyx eczema. Nine patients (18%) had healed completely during the 6 years follow-up. Seventeen patients (34%) stated that the eczematous activity was unchanged, 21 patients (42%) stated a decreased eczematous activity, and 3 patients (6%) an aggravation. In the group "Non-pompholyx eczema" (13 patients) 1 patient had evolved a pompholyx, 10 patients (77%) had healed and the remaining 2 patients had but a mild hand dermatitis. The difference between the proportions of patients healed in the "Non-pompholyx material" (77%) and in the group "All pompholyx patients" (18%) is highly significant ($p < 0.001$).

Occupation at début of hand eczema and effect of occupational change

No particular occupation predominated at the start of hand eczema. In fact, 19 different occupations were represented among the patients. Twentyfive patients (19 in the group "All pompholyx patients" and 6 in the group "Non-pompholyx patients") changed

their profession. Nine patients retired (3 at the regular age of 65, 6 before that age because of other diseases). Thirteen patients changed their profession mainly of socioeconomic reasons. The remaining 3 patients were considered occupational according to Swedish law. No particular change in healing frequency and eczematous activity was observed in the patients who changed their profession compared to those who didn't.

Metal sensitivity, patch test reaction, immediate type contact dermatitis, concomitant cobalt allergy

The results of the patients' history of metal sensitivity and reaction to the patch test to NiSO_4 are presented in Table 2. Fiftyseven patients (91%) had a typical history. One patient who earlier had a positive history of metal sensitivity claimed that she had got rid of this; the patch test however was positive. Five patients were uncertain about their metal sensitivity; 2 had a positive patch test, 2 were negative even by intracutaneous testing with 0.1% NiCl , and the last patient was not tested. In all, 54 patients were tested and 52 were positive.

In the total material 11 of 63 patients (10 in the group "All pompholyx patients" and the one who had switched to pompholyx) had a history of immediate type contact dermatitis when handling different food-stuffs (potatoes, tomatoes, onions, oranges, lemons, cheese, shell-fish and meat). Specific testing was not carried out in these patients. None of the patients with immediate type contact dermatitis were healed.

In the present material 21 patients had a concomitant cobalt allergy at the original patch testing (Christensen & Möller 1975). Seventeen patients belonged to the group "All pompholyx patients", and the remaining 4 to the group "Non-pompholyx patients". Of the 21 cobalt hypersensitive patients only 4 (19%) were healed. In comparison, 15 of 42 patients (36%) without cobalt hyper-

sensitivity had healed; the difference is not statistically significant. In the group "All pompholyx patients", 1 of the 17 patients (6%) with a concomitant cobalt allergy was healed. Compared to 33 patients without cobalt allergy among whom 8 patients (24%) were healed the difference is not statistically significant.

Atopic history, serum IgE

In the material 28 patients (44%) with a history of personal and/or family atopy were found. Twentyfive patients (50%) were found in the group "All pompholyx patients" and 3 patients (23%) in the non-pompholyx group. The difference between these two groups is not statistically significant. Fifteen patients were found to have a history of personal atopy, while 13 had a family history of atopic disease. Of the 25 atopics in the "All pompholyx group" 3 were healed, while 2 atopics of 3 in the "Non-pompholyx group" were healed. In all, 5 of 28 (18%) were healed compared to 14 of 35 (40%) non-atopics. This difference is slightly significant ($p < 0.05$).

Among the 11 patients with immediate type of contact dermatitis there were 7 patients (64%) with personal and/or family atopy. Compared to 21 patients (40%) with personal and/or family atopy among 52 patients without immediate type contact dermatitis there was no statistical difference.

The result of the PRIST determination is illustrated in Fig. 1. PRIST was estimated in 52 patients in the material (group I). Fiftytwo females from a health screening material, mean age 45 (31-49), served as controls (group II). With regard to atopic history and prognosis of hand dermatitis the material

(group I) was compared to the following subgroups; group III: 13 patients with personal atopy; group IV: 30 patients with active pompholyx; group V: 22 patients healed or with non-pompholyx eczema; group VI: 8 patients with immediate type contact dermatitis. No statistically significant difference was found between PRIST values of the groups I/II, I/III, IV/V, I/VI, III/VI and II/VI. The difference between the groups II/III was slightly significant ($p < 0.02$). Among the 52 PRIST values determined in patients with nickel allergy and hand eczema 10 were higher than 100 units/l compared to 4 in the control group of 52 females in the health screening material. This difference is not significant. Among the patients classified as personal atopics only 5 of 13 had a PRIST higher than 100 units/l.

Therapeutical effect of topical corticosteroids

In the group "All pompholyx patients" 34 patients were able to evaluate the effect of topical corticosteroid treatment. Seventeen patients claimed that local steroids had some beneficial effect on their hand eczema, 16 patients claimed no effect and 1 patient experienced deterioration. The patients' evaluation was the same independent of the potency of the corticosteroids.

DISCUSSION

In nickel sensitive subjects different types of clinical expressions seem to exist. First, there is a large group of subjects comprising around 10% of the grown-up female population (Menné 1978, Prystowsky et al. 1978, Kiefer 1979,

Magnusson & Möller 1979, Peltonen 1979) in which the majority are "healthy" persons with a metal hypersensitivity but with no hand dermatitis. Secondly, there is a group of patients with nickel allergy and hand eczema. Some population studies (Menné 1978, Peltonen 1979) indicate that 20-45% of nickel sensitive patients at some time or other develop dermatitis of the hands, but compared to the high prevalence figures in "healthy" women, this proportion seems very high.

The present study has shown that hand dermatitis in nickel sensitive female patients seems to follow two courses: a mild transient, non-disabling and a chronic, more disabling. Fregert (1975) found no healing among 29 nickel sensitive females with hand eczema in a 10 year occupational material, whereas 30% in the present material were healed after 6 years. The prognosis in the present material is obviously better than in an occupational material.

In the literature on nickel allergy and hand eczema too little reference has been made to the different clinical types. The present work is the first attempt to determine the prognosis in relation to different types of hand eczema. The fact that only 9 of 50 patients with pompholyx were healed compared to 10 of 13 patients with non-pompholyx eczema clearly shows that the prognosis in patients with nickel allergy and hand eczema of the pompholyx type is worse than in patients with other types of nickel hand eczema. In fact, this correlation was indicated in our previous study (Christensen & Möller 1975), where the mean duration of hand eczema in pompholyx patients was found to be 9.3 years against 3.0 years in the non-pompholyx patients. Actually, the majority of patients with non-pompholyx eczema had but short periods of hand dermatitis with minor personal discomfort.

Traditionally, occupations as hairdressers, cashiers shop assistants, seamstresses, metal industry and restaurant workers are considered occupations with heavy nickel exposure. Marcussen (1960) and Menné & Bachmann (1979) state that dermatitis in nickel sensitive patients in about 40-60% starts on the hands in occupations with heavy nickel exposure. In the original material (Christensen & Möller 1975) metal sensitivity and hand eczema started simultaneously in 15 of 66 patients, only 1 patient did not notice metal sensitivity until after start of hand eczema. Fregert (1975) found 19% of nickel sensitive female patients occupied in cleaning work. Occupations with heavy nickel exposure were not particularly common at the start of hand eczema in the present material. Probably these different proportions to a certain extent depend on material selection, Menne's & Bachmann's comprising patients of a Danish permanent disability pension material and Fregert's being a pure occupational material. The present material consists of patients from our out-patient department, the only dermatological department of an urban area with many different types of occupation. Malmö has a health-care system and a tradition in the population, making our department the place where the majority of patients with skin diseases apply.

It is shown (Fregert 1975, Reichenberger 1977, Menné & Bachmann 1979) that changing occupation or retiring of patients with severe hand dermatitis does not result in a higher frequency of healing than continuing in the same occupation. The same conclusion may be drawn from my results. Even if most of the patients did not change their occupation because of their hand dermatitis, the prognosis was not found to be related to change of occupation or retirement. However, atotics with nickel

allergy and pompholyx and an additional immediate type contact dermatitis have a bad prognosis. Furthermore, if these patients are occupied in wet occupation (Fregert 1975), several criteria indicating that their eczema hardly will heal are fulfilled, and they should be transferred to non-traumatic and non-sensitizing occupations.

As in the original study (Christensen & Möller 1975) a good correlation was found between a history of metal sensitivity and a positive patch test reaction. Of the 52 patch tested positive patients only 1 patient completely denied hypersensitivity. The 2 patients who had negative patch tests were both classified as being uncertain about their metal sensitivity history. Cronin (1972) and Kiefer (1979) both observed that about 35% of the patients with a positive patch test reaction to nickel never had experienced dermatitis under metal objects. On the other hand Peltonen (1979) and Prystowsky et al. (1978) report a very strong correlation between positive patch test reactions to nickel and metal sensitivity, which agrees with my results. Retesting the patients after 7 - 9 years showed that still 96% (50 of 52) reacted with a positive patch test. It can therefore be concluded that an acquired nickel hypersensitivity seems to last at least one decade. By retesting 27 patients with nickel hypersensitivity after 1-20 years (mean 7.6) Marcussen (1959) found that only 1 patient had become negative. Fisher and Shapiro (1956) found by retesting 40 patients after 2 - 17 years that 36 patients retained their nickel sensitivity. These results agree with the findings in the present material.

Two patients had negative reactions both by epicutaneous and intracutaneous testing with nickel, and may therefore be suspected to have lost their nickel hypersensitivity. Both patients had healed; one of the patients had a history of personal atopy with PRIST 550 units/l and the other patient a heavy family atopic history. It is possible that the patients' original patch test reactions which qualified them into the material (Christensen & Möller 1975) were false positive "porite" reactions, often seen in atopics.

In the material 11 patients had a history of immediate type contact dermatitis when handling different food-stuffs. The combination of immediate and delayed type contact dermatitis seems to influence the prognosis to the worse since none of the 11 patients were healed during the 6-year follow-up. None of the 11 patients had felt any discomfort by handling food-stuffs prior to development of hand dermatitis. Hjorth & Roed-Petersen (1976) and Krook (1975) have shown that immediate type reactions are easier provoked in previously affected skin; this observation agrees with my patients' history. Atopic history was not found correlated to immediate type contact dermatitis.

Menné & Bachmann (1979) indicates that a coexisting nickel-cobalt allergy results in a worse prognosis than if nickel allergy occurs alone. Also my results indicate such a relationship, but statistically significant differences could not be obtained.

A rather high proportion of personal and/or family atopy was found compared to the primary material (Christensen & Möller 1975) where only 7 patients with personal atopy are reported. It is possible that the time elapsed between the two investigations has made the patients more aware of the problem.

When the patients' history is the only criterion used in classifying a patient as atopic, some patients with non-allergic bronchial asthma or vasomotoric rhinitis may be misinterpreted as atopics. The fact that IgE in only 5 of 13 patients with personal atopy was higher than 100 units/l may mean that some of the patients in the present material classified as atopics in fact were not true atopics according to Johansson (1976).

Actually, the degree of atopy is usually not evaluated in the dermatological literature dealing with atopy and associated diseases. It seems more and more obvious that a score system, including factors as degree of atopic disease, degree of heredity, cutaneous allergic and non-allergic test reactions, provocation tests, PRIST values and RAST specificity, should be taken into account when classifying an atopic individual. The manifestations of atopy in my patients with both personal and family atopy were considered rather mild. The fact that 10 patients in the material compared to 4 in the control material had IgE values higher than 100 units/l suggest however that atopy is more common in a material with nickel allergy and hand eczema, than in a control material:

A high frequency of atopy in patients with pompholyx was reported by Oddo & Témime (1968) but no reference was made to nickel allergy. The relationship between atopy and nickel allergy is debated in several papers. Epstein (1956), Dobson (1963), Watt & Baumann (1968) found a marked positive correlation between nickel allergy and atopy whereas Calnan (1956), Wilson (1956), Marcussen (1957) and Caron (1964) found no such connection. Wahlberg & Skog (1971) found a high frequency of family atopy in relations to nickel hypersensitive patients. However, in the papers mentioned

the relationship between nickel allergy and hand eczema is not stated and comparison with the present material cannot be done. Even if the proportion of atopics among patients with pompholyx was not significantly higher than among patients with non-pompholyx eczema the figures suggest that atopy somehow is correlated to pompholyx. Probably a more extended material could clarify this question. However, atopy was found to be slightly correlated to healing, making the prognosis more serious.

Determination of serum IgE is useful in atopic patients and the value usually correlated positively to the degree of atopic disease (Johansson 1976). In the present material no significant difference was found in PRIST values compared to those of a control material. By comparing different groups within the material PRIST was not found to be of any use in evaluating the degree of personal atopy or predicting prognosis of hand eczema in nickel sensitive patients.

Treatment with topical corticosteroids in patients with nickel allergy and pompholyx was not always found beneficial. Therefore, long term prescription of these drugs with their well-known side effects should certainly be reconsidered.

ACKNOWLEDGEMENT

The author is grateful to Björn Edman for skilful statistical assistance.

Table 1. Diagnosis made and eczematous activity evaluated in 63 patients with nickel allergy and hand eczema in a 6 year follow-up study.

Diagnosis 1973-74	n	Diagnosis 1980	n	Eczematous activity 1974-80	n
Pompholyx only	41	Pompholyx only 28 Pompholyx + other eczema 1 Non-pompholyx eczema 3 No eczema 8	40	None (last 2 years) 8 Unchanged 15 Decreased 15 Increased 2	
Pompholyx + other eczema	10	Pompholyx only 0 Pompholyx + other eczema 7 Non-pompholyx eczema 2 No eczema 1	10	None (last 2 years) 1 Unchanged 2 Decreased 6 Increased 1	
All pompholyx patients	51	Pompholyx only 28 Pompholyx + other eczema 8 Non-pompholyx eczema 5 No eczema 9	50	None (last 2 years) 9 Unchanged 17 Decreased 21 Increased 3	
Non-pompholyx eczema	15	Pompholyx only 0 Pompholyx + other eczema 1 Non-pompholyx eczema 2 No eczema 10	13	None (last 2 years) 10 Unchanged 0 Decreased 2 Increased 1	
Total material of hand eczema	66	Pompholyx only 28 Pompholyx + other eczema 9 Non-pompholyx eczema 7 No eczema 19	63	None (last 2 years) 19 Unchanged 17 Decreased 23 Increased 4	

Table 2. History of metal sensitivity and results of epicutaneous retesting of patients in a 6 year follow-up study.

	n	History of metal sensitivity	n	Patch test to nickel	n
Total material of hand eczema 1980	63	Positive	57	Tested	54
		Negative	1	Positive test	52
		Uncertain	5	Negative test	2

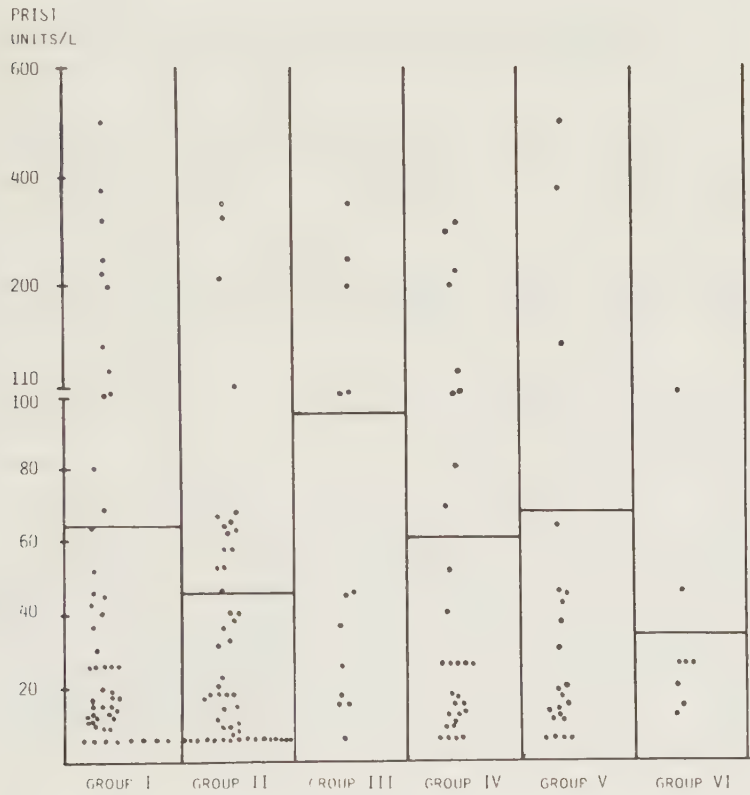


Fig. 1. Serum IgE in 52 patients with nickel allergy (group I), different subgroups (III-VI) and in a control material (group II). The mean value for each group is indicated as a transversal line.

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External and internal exposure to the antigen in the hand eczema of nickel allergy

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A provocation study was performed in twelve female patients with contact allergy to nickel and hand eczema of the pompholyx type. Intense handling of nickel-contaminated metal objects did not induce any visible eczematous activity. Oral administration of nickel in a double-blind test provoked an aggravation of the hand eczema in nine of the twelve patients, and in seven of the patients this was accompanied by secondary eruptions including outbreaks of earlier, healed eczema. The nickel dose given is probably in the upper limit of the presently known daily intake of the metal, but should be considered to be within the physiologic range. It is concluded that ingestion of small amounts of nickel may be of greater importance in maintaining the hand eczema than external contacts with the metal.

Key words: contact allergy – nickel – hand eczema – provocation.

Received for publication September 30, 1974

In a previous publication (Christensen & Möller, in press) the hand eczema so commonly associated with contact allergy to nickel in women was clinically characterized. The most frequently occurring eczema was a pompholyx, i.e. a recurring itching eruption with deeply seated, fresh or inactive vesicles, with some or no erythema, localized on the palms, volar aspects and sides of fingers, sometimes with similar lesions in the soles. The clinical pattern with its capricious course was found hardly compatible with the traditional concept of the eczema being elicited by repeated contact with the metal. This prompted an experimental study comprising external as well as internal stimuli to provoke the hand eczema.

Material and Methods

The study was performed in twelve female patients aged 21–60 years with a contact allergy to nickel and a hand eczema of the pompholyx type (Christensen & Möller, in press). Ten of the patients had pompholyx only, while two had an additional dermatitis of the allergic contact eczema type. A concomitant allergy to cobalt was present in four of the twelve patients. All patients had noticed a hypersensitivity to metals (earrings, brassière clips, bracelets, zips, suspenders, etc.) and the contact allergy had been verified with epicutaneous tests not later than 3 years previously. All subjects were out-patients having earlier received the regular information with regard to the pos-

sibilities of avoiding nickel-containing objects.

External exposure. A bowl was prepared containing about a kilogram of nickel-containing objects; these were mainly Swedish silver coins in circulation, released in the year 1968 or later, but also some paper-clips and keys. The nickel content of the coins is 25 % and their surface is always heavily contaminated with the metal (Bang Pedersen et al. 1974). The objects were positive in the qualitative nickel test (Fisher 1973).

The patients were instructed to dig their hands into the bowl, thereby actually washing them with the nickel objects. This intense contact lasted for 6 minutes. The patients were not allowed to wash their hands for the following 2 hours. A clinical examination was performed before the provocation and 24 hours later.

Internal exposure. This test was carried out as a double-blind study. The patients obtained either a lactose-containing placebo capsule or one with lactose and 25 mg nickel sulfate ($\text{NiSO}_4 \cdot 6 \text{H}_2\text{O}$) with a nickel content of 5.6 mg. At a later occasion the test was repeated with the reverse medication. A clinical examination was performed before the provocation, and 6 hours as well as 30 hours later.

Registration. With both types of provocation the test occasion was chosen to be a time when the eczematous activity was low or absent, also avoiding the monthly period. In order to facilitate registration of the vesicular eruption the volar aspect of each hand was divided into 17 areas limited by the natural furrows. The border lines, traced with a felt pen, remained visible throughout the test period. The individual vesicles were counted under a magnifier ($\times 2$) and a daylight lamp. This registration was performed

at the same time as the general clinical examinations when signs and symptoms of secondary eruptions were looked for.

Results

The outcome of external provocation with nickel is shown in Table 1. No increased activity of the hand eczema, as expressed by amount of vesicles, was observed in any of the cases. Three patients complained of itching palms 10 minutes, 4 hours and 8 hours after the test, without visible changes, however.

Before breaking the code, nine patients (A-I) were considered to have reacted positively to the internal provocation, and three (J-L) negatively (Table 2). After breaking the code it was found that all nine positive patients had obtained nickel when reacting. In the positive responses (Fig. 1), there was a great increase in the number of hand vesicles with a mean of 8 times the number before the test, and all the patients complained of more or less itching of the palms (after an average of 10 hours) and at the sites of secondary eruptions. Among the

Table 1. The total number of vesicles, and itching, on the volar aspects of both hands during the external provocation with nickel in 12 patients

Patient and age	Number of vesicles		Times increase	Itching of palms
	At start	At 24 h		
A 29	20	20	0	—
B 31	72	68	0	—
C 43	109	110	0	—
D 30	10	9	0	—
E 29	Test refused			
F 48	66	64	0	—
G 52	10	11	0	—
H 60	214	220	0	+
I 21	248	248	0	—
J 38	22	22	0	—
K 37	0	0	0	+
L 53	12	8	0	+

Table 2. The total number of vesicles and itching on the volar aspects of both hands during the internal provocation with placebo and nickel in 12 patients

	Patient	PLACEBO			NICKEL		Times increase	Itching of palms
		Number of vesicles At start	Number of vesicles At 30 h	Times increase	Number of vesicles At start	Number of vesicles At 30 h		
Positive cases	A	20	20	0	30	250	8.3	++
	B	63	72	0	17	273	16.1	++
	C	120	113	0	300	947	3.2	++
	D	10	11	0	65	306	4.7	++~
	E	26	28	0	28	452	16.1	++
	F	70	66	0	55	180	3.3	+
	G	8	10	0	38	357	9.4	++
	H	226	214	0	311	872	2.8	+
							m 8.0 range 2.8-16.1	
	I	239	248	0	220	oozing, not countable	?	++
Negative cases	J	2	2	0	0	0	0	-
	K	0	0	0	0	0	0	-
	L	11	12	0	9	8	0	+

negative cases one patient complained of palmar itching 11 hours after nickel administration but was considered negative because of the lack of objective changes.

Secondary eruptions characterized by a flare-up at earlier sites of eczema, or in other locations, occurred in seven of the nine positively reacting patients (Table 3). They did not occur in any of the three negative patients. The flare-up reactions were observed at the sites of previous patch tests, on the earlobes, in areas corresponding to brassière clips, zips and suspenders. These reactions were usually much larger than the patient could remember or than was noted in the records. In six patients there was an interval of anything from 6 months to 10 years between the old eczema patch and the flare-up reaction.

The secondary eruptions occurring at other sites were always symmetric, having the appearance of a macular or papular toxicoderma, usually located at the extremities (Table 3).

The time interval for the earliest symp-

toms of a positive response to internal provocation varied between 1 and 20 hours (Table 3) and agreed fairly well with the start of the palmar reaction.

Some individual observations. Patient G, with a 15-year history of cheiropompholyx and a similar eruption in her soles during the previous 3 years, reacted with an increased number of vesicles here as well as in her hands. Patient B gave a history of hand eczema during the previous 10 years and recurrent urticaria for 5 years. When given the nickel capsule, she reacted with a maculo-papular exanthem with the addition of some weals. Patient I had had her hand eczema for the previous 3 years and 3-4 annual bouts of urticaria of unknown origin for the same period. One hour after the nickel administration there was itching and an increased number of vesicles in her palms. After 3-6 hours, a generalized itching reaction developed including oedematous swelling of her hands, wrists and eyelids, asymmetric dissemination of weals accompanied by tinnitus and dizziness. Simultan-



Fig. 1. Pompholyx in nickel allergy provoked by oral administration of the antigen.

ously the pompholyx progressed to a diffuse, oozing dermatitis. The blood pressure was 90/70, the pulse 110/min. She was treated with parenteral antihistamine and hydrocortisone at 6 and 14 hours. At 18 hours the patient had developed, in addition to the urticaria and the pompholyx, a maculo-papular rash symmetrically on the neck, arms, abdomen and thighs. On another occasion patient I was given 0.44 mg nickel (about 1/10 of the usual dose) and reacted with a few scattered weals and an intensified pompholyx.

Discussion

A positive patch test to nickel in a patient with hand eczema is usually considered relevant (Wilkinson 1972). Even when the diagnosis is followed by thorough instructions on how to avoid nickel contacts, the prognosis is poor (Christensen & Möller, *in press*). A careful questioning of these patients shows only a small correlation be-

tween metal contact and worsening of their hand eczema. This impression is corroborated by the findings in the present study in which an intense contact with nickel objects in no case induced an exacerbation. Three patients complained of palmar itching after this provocation, which might be interpreted as an effect of suggestion. This iatrogenic reaction is further illustrated by the refusal of patient E to participate in the test.

The question may be asked if the external provocation was sufficient with regard to quantity of nickel and to exposure time. It has been found that hands are contaminated with nickel from circulated as well as ether-washed silvercoins (Bang Pedersen *et al.* 1974). An exposure time of 5 minutes was found quite sufficient and could be equalled with regular handling of coins for 4 hours. Our external provocation is thus considered relevant. It should therefore be concluded that regular handling of nickel-

Table 3. Occurrence of flare-up reactions and other secondary eruptions in nine patients with a positive response to internal provocation with nickel.

Patient	Time interval (h) for the earliest symp- toms of a pos- itive response to provocation	Flare-up of earlier healed eczema	Eruptions outside flare-up sites
A	9	+	
B	10	+	Elbow flexures, armpits, groins, inside of thighs
C	11	+	Elbow flexures, forearms
D	9	+	Elbow flexures, forearms
E	7	+	Elbow flexures, forearms, thighs
F	20	—	—
G	8	+	Forearms, soles
H	10	—	—
I	1	+	Generalized (see text)

coated objects only rarely induces a recurrence of a pompholyx. On the other hand, it is certainly possible to elicit an allergic contact eczema to nickel in the palm. For this to succeed, however, an occlusive patch test is required (personal observations).

It is a common experience that an allergic contact eczema may flare up following accidental or experimental ingestion of the allergen. For reviews on such "endogenous contact eczema", see Fisher (1966), Piriälä (1970), and Cronin (1972). In some of these cases, viz. with neomycin (Ekelund & Möller 1969), chromate (Fregert 1965), penta-decyl catechol (Kligman 1958) and cinnamon (Piriälä 1970) an aggravation of pompholyx has been mentioned in particular. This knowledge motivated the internal provocation in this type of recurrent pompholyx which gave a positive response in nine of twelve cases. The results may be compared with a similar oral provocation with neomycin, positive in ten of twelve cases, and with hydroxy-quinoline, positive in six out of nine cases (Ekelund & Möller 1969).

The present reactions were similar to the patients' ordinary eczematous eruptions but there was a great variety in intensity. This

was particularly illustrated in those patients who had secondary eruptions. Apparently, the individual sensitivity to the given nickel dose varied greatly (Table 2); in the one extreme there were two patients with 3 times increase of palmar vesicles and no secondary eruptions, in the other there were two patients with 16 times increase plus secondary eruptions, even including urticarial rash. It seems possible that the three non-responsive patients would have reacted to a higher dose. It may thus be assumed that the patients' recurrent hand eczema is maintained by intermittent ingestion of small amounts of nickel. The varying clinical picture is then probably an expression of the ingested dose and, possibly, the prevailing state of immunity.

Nickel is ubiquitous in nature and measurable amounts occur in human blood, urine and sweat (Hohnadel et al. 1973). The average daily intake through American food has been estimated to be 0.3 – 0.6 mg (Schroeder et al. 1962). Geographical differences prevail and a study on the daily intake of nickel in 17 subjects performed in Dalby—a town only 30 km from Malmö (where the study was being carried out)

(Dencker et al. 1971) showed a mean value of 0.76 mg with a range of 0.20 – 4.46 mg. Up-to-date studies on the nickel content of individual food stuffs have not been performed and it is possible that several factors are of importance such as contamination from metal containers and utensils, fertilizers etc. It may thus be concluded that the dose of 5.6 mg nickel given in the present investigation could be considered physiologic.

A theoretical consequence of the present findings is that the hand eczema in nickel allergy should be considered a secondary eruption or it may be a flare-up reaction. In that case the eruption may not necessarily be elicited by way of cell-mediated immunity, but, as has been postulated for the experimental chromate dermatitis in the guinea-pig, by humoral antibodies (Polák et al. 1973).

A practical consequence of the present findings is that the medical problem of our patients can be solved only to a small degree by avoiding external contact with nickel. It appears important to diminish the primary sensitization to nickel in the population in order to stop the development to hand eczema. With this eczema established the accidental ingestion of the metal should, if possible, be decreased. The frequent development to a "dyshidrotic" eczema in chromate hypersensitivity (Reichenberger 1972) may imply an analogous reaction pattern, warranting further investigation.

Acknowledgement

This study was supported by a grant from "Svenska livförsäkringsbolags nämnd för medicinsk forskning".

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Release of nickel from cooking utensils*

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The release of nickel to boiling water from new and used saucepans of different material was measured. No nickel was released from aluminium, teflon and enamel. Certain amounts of nickel were released from stainless steel, but only at acid pH.

Key words: Cooking utensils – hand eczema – nickel – stainless steel.

Received for publication April 1, 1978

Contact allergy to nickel often results in a chronic hand eczema, mainly of the pompholyx type (Christensen & Möller 1975a). We were able to show that nickel dermatitis could be activated by oral administration of the antigen (Christensen & Möller 1975b). Thus, accidental ingestion might explain the chronicity and periodic exacerbations of the eczema.

Among possible sources for such ingestion it is known that varying amounts of nickel occur in our food (Dencker et al. 1971, Kirkpatrick & Coffin 1974). This contamination may originate from the native foodstuffs (Schroeder et al. 1962) but a certain amount may also be added when cooking and storing (Thomas et al. 1974). It thus seemed warranted to study the possible release of nickel from commonly used cooking utensils in Sweden.

Material and Methods

Experiments were performed with freshly

produced, one-liter saucepans from two Swedish distributors (Nils-Johan and Kooperativa Förbundet, Stockholm, Sweden). There were six saucepans of stainless steel (chrome/nickel 18/8), two of aluminium, two of aluminium coated with teflon, and two of aluminium coated with enamel. Also included in the study were 15 used saucepans of stainless steel. Before every experiment the saucepans were washed with detergent and tap water, and rinsed three times with distilled and deionized water (DDW).

The saucepans were filled with 600 ml DDW which was allowed to evaporate by boiling to a final volume of 25–30 ml. The boiling time was approximately 80 min. Before boiling, most water samples were adjusted to pH 5.0, 3.5, 3.2, or 3.0 with hydrochloric acid (Merck p.a.) or to pH 11.0 with sodium hydroxide (Aristar, BDH). The pH value before and after boiling was determined with a pH meter PHM 26 C, Radiometer AS, Copenhagen, Denmark.

* Presented at the meeting of the Swedish Medical Association, Stockholm, December 2, 1977.

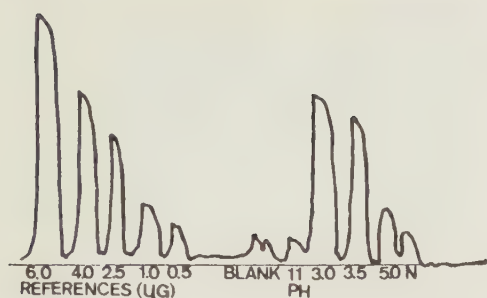


Fig. 1. Recording of the amount of nickel in references (left) and in water of different pH boiled in a stainless steel saucepan (right).

To the 30-ml water sample, 10 ml of a potassium biphthalate-hydrochloric acid buffer pH 2.4 was added. The samples were adjusted to a final pH of 2.5 with either HCl or NaOH. After chelating with 2 ml 2 % ammonium pyrrolidine dithiocarbamate (BDH), the samples were extracted to an organic phase with 5 ml methylisobutylketone (BDH). The nickel concentration was assayed by atomic absorption spectrophotometry (Perkin-Elmer 303). Water samples containing known amounts of nickel chloride (1 mg/ml BDH) carried through the method were used as a reference standard. For each pH level investigated duplicate blanks were used consisting of DDW boiled in acid-washed glass and carried through the method.

In one series of five experiments regular kitchen salt to a concentration of 1 % was added to DDW of neutral pH before boiling in a stainless steel saucepan, and in another series sodium chloride (Merck p.a.) was used

similarly. The same solutions boiled in acid-washed glass served as controls.

Recovery of 10 μ g nickel chloride added to 600 ml water *before* boiling and carried through the method was 90.0 and 87.5 % in two assays. Recovery of 20 μ g in four experiments was 90.5, 87.5, 90.5 and 87.5 % (mean 89.0). Recovery of 20 μ g nickel chloride added to the 30-ml water sample *after* boiling and carried through the method was 95.0, 93.8, 93.8, 93.8, 90.5, 90.0 % in six assays (mean 92.8 %).

Student's t-test was used for statistical analysis.

Results

When boiling water in saucepans of aluminium, as well as enamel- and teflon-coated aluminium, negligible amounts of nickel, within the error of the method, were registered at all pH levels tested. The same negative result was obtained with stainless steel saucepans at alkaline and neutral pH.

When boiling water in stainless steel saucepans at acid pH, nickel was released in amounts that were calculated on the basis of references and blanks (Fig. 1). Measurable nickel amounts were registered with new saucepans at every acid pH tested, particularly at pH 3.5 and 3.0 (Table 1). This tendency is also seen in Fig. 1. The used saucepans, tested at pH 3.2, yielded nickel in amounts similar to the new ones. At each pH, the released amounts showed a large variation.

In order to examine the tendency of in-

Table 1. Release of nickel to boiling water in the six new and the 15 used stainless steel saucepans

Saucepans	pH		Mean	μ g Ni	Amount of assays
	at start	at end (approx.)		Range	
new	5.0	4.0	6.0	0.2-22.9	17
new	3.5	2.3	12.4	1.1-38.7	18
new	3.0	2.0	14.7	3.9-22.5	9
used	3.2	1.8	20.3	2.8-34.0	30

Table 2. Release of nickel (μg) from two new stainless steel saucepans. The examinations were carried out by boiling alternatively at lower and higher pH

Saucepan A		Saucepan B	
pH 5.0	pH 3.2	pH 5.0	pH 3.2
0.50	1.32	0.35	6.50
0.25	5.00	0.75	7.50
0.25	2.50	0.75	5.00
0.50	2.00	0.75	4.00
0.00	2.00	0.25	5.00
m 0.30	2.57	0.57	6.00
P < 0.01		< 0.001	

creasing nickel release at decreasing pH, two saucepans were selected for repeated boiling at pH 5.0 and 3.2. The results presented in Table 2 show that a higher amount of nickel is released at pH 3.2 than at pH 5.0.

The two salt solutions did not release any nickel from the stainless steel saucepan.

Discussion

The boiling experiments have shown that nickel is not released from saucepans of aluminium, enamel and teflon to water of varying pH. Cooking utensils of these materials may thus be safely recommended to patients with nickel allergy.

When boiling water at neutral pH in stainless steel saucepans, this material also appeared safe. However, when the pH was lowered, appreciable amounts of nickel were leached out into the boiling water, from new as well as used saucepans (Table 1). It was even shown that the amounts released were positively correlated with the acidity of the water (Table 2). As a consequence, patients with nickel allergy should avoid stainless steel cooking utensils since several foodstuffs, such as lingonberries, rhubarb and apples, may provide an acid milieu (pH 2.8–3.2) during processing.

Earlier statements on the hazard of stainless steel materials (Fregert 1974, Katz & Samitz 1975) have thus been experimentally confirmed. It was not possible to determine the pH level at which nickel release started and where it was maximal, since the acidity of the water increased during our boiling procedure (Table 1).

The amount of nickel released from cooking utensils in the present study was fairly small in comparison to the dose used in oral provocation (Christensen & Möller 1975b). Thus, the clinical relevance of this type of contamination might be questioned. Great variation in sensitivity was, however, observed in the patients of our provocation study and therefore even small amounts of nickel may be of importance in sensitive subjects. This is also corroborated by a recent report (Rudzski & Grzywa 1977).

Acknowledgments

We are grateful to Assistant Professor J.-O. Jeppsson, Department of Clinical Chemistry, for putting the atomic absorption spectrophotometer at our disposal and for reviewing the manuscript. Cooking utensils were kindly delivered from Nils-Johan and Kooperativa Förbundet, Stockholm. The study was supported by a grant from Svenska livförsäkringsbolags nämnd för medicinsk forskning.

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Nickel Concentration of Blood and Urine After Oral Administration*

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ABSTRACT

Nickel concentration in serum and whole blood as well as nickel excretion in urine was assayed at different time intervals before and after ingestion of nickel sulfate in eight healthy volunteers during a three days study. The peak level of nickel in blood was reached 2.5 hours after nickel ingestion and the maximal urinary excretion of nickel was during the first eight hours after ingestion. Great individual variations in nickel concentrations in blood and of nickel excretion in urine were observed. Analysis of nickel in both urine and serum reflects ingestion of a soluble nickel salt, but urine seems to be most reliable to follow.

Introduction

The interest in nickel concentrations in body fluids has risen among dermatologists after it was shown that ingested nickel can aggravate the dermatitis in a nickel sensitive patient.⁴ Several papers reflect that interest.^{6, 8, 11, 14, 15, 19} Some papers indicate that the activity of the nickel dermatitis is positively correlated to the nickel excretion in urine.^{8, 11, 15}

Among toxicologists, occupational physicians and oncologists, analysis of nickel concentrations in body fluids has been performed extensively during several years to monitor environmental and occupational exposures to different nickel compounds.^{1, 2, 9, 13, 21}

In most of the papers published, little attention has been directed to the specific times at which specimens of body fluids should be collected for nickel analysis or the knowledge of nickel metabolism has been insufficient for predicting the optimal times or intervals for collection of samples. The present study was performed to get a better understanding of the distribution of an ingested soluble nickel salt in blood and urine.

Material and Methods

There were eight healthy volunteers, six females and two males, aged 21 to 32 years, with no history of metal hypersensitivity. Each subject was instructed to drink and eat about the same amount and type of liquids and foods at the same period during the study. Measurements of nickel concentration in liquids and foods were not performed.

Day 1. A venous blood sample of 8 ml

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was taken at 8:00 a.m., 1:00 p.m. and 3:30 p.m. by puncturing the elbow flexural veins. Three ml of the blood sample were put into a 10 ml heparinized test tube and stored at -20°C for later analysis in whole blood. The other 5 ml of the sample were centrifugated, and the serum was taken and stored frozen until analysis.

Day 2. At 8:00 a.m., each subject ingested a capsule containing 25 mg nickel sulfate ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) in lactose, the nickel content being 5.6 mg. Eight ml venous blood were taken at 8:00, 9:00, and 10:30 a.m., at noon and at 2:00 and 3:30 p.m.

Day 3. The same amount of venous blood was taken at 8:00 a.m. and 3:30 p.m. The blood samples taken on days 2 and 3 were treated as mentioned for day 1.

Urine voided 8:00 a.m. to 4:00 p.m., 4:00 to midnight, and midnight to 8:00 a.m. was collected in 500 ml polyethylene acid washed bottles every day during the three days study. The volume was estimated, and 5 ml from each sample were taken and stored frozen until nickel analysis.

The analyses were carried out on an IL 551* atomic absorption spectrophotometer equipped with an IL 555 graphite furnace and rectangular graphite cure. The spectrophotometer is a double beam instrument with deuterium arc lamp for background correction. The instrument is equipped with a computer unit. The background corrected or uncorrected signal as well as peak heights and peak areas are displayed on a monitor. The samples were analysed in microboats and pre-ashed outside the graphite furnace. A special probe plate for 16 microboats was used,¹² and the samples were pre-ashed in an ordinary laboratory oven.

All the analyses carried out in this work were direct determinations. No dilution of the samples, addition of matrix solvents, acids or other modifications of the samples were made. Thirty μl of blood, serum or urine were pipetted into the graphite

microboats. The microboats were placed in the laboratory oven. Urine samples were dried at 100°C for five minutes and ashed at 600°C for two minutes. Blood and serum samples were dried at 100°C for five minutes and ashed at 700°C for two minutes. Finally, the samples were analysed in the graphite furnace. All samples were assayed in duplicate and mean values of the two results were accepted. The reproducibility of these assays was 3.3 to 10 percent.

Statistical techniques included testing by Student's paired *t*-tests and computations of correlation coefficient and linear regression analysis by the least-squares method. Even computations according to rank sum test were applied.

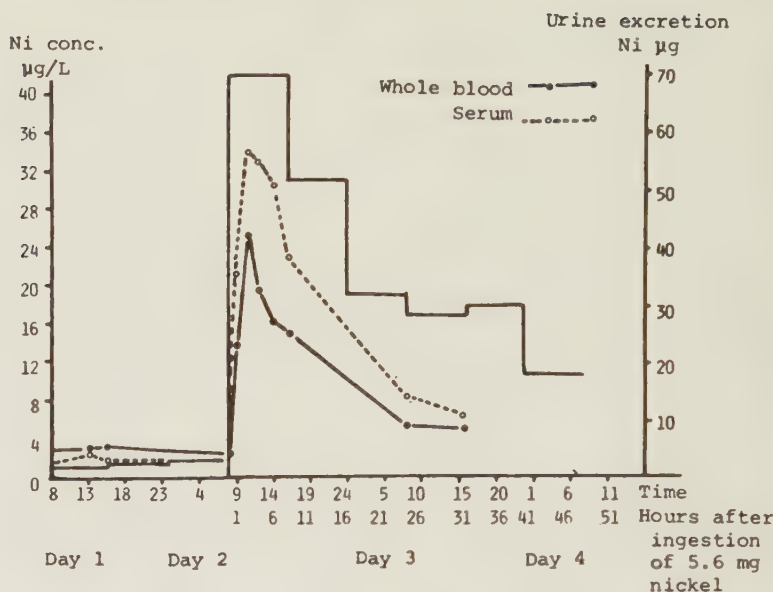
Results

The mean values for nickel concentration in serum, whole blood and nickel excretion in urine during the three days study are illustrated in figure 1. The concentrations in blood and urine before and after ingestion of nickel together with mean values and standard deviations are listed in table I. The mean peak concentration of nickel in serum and whole blood was reached at 10:30 a.m., 2.5 hours after nickel ingestion. The time for peak values was 9:00 o'clock in one subject and noon in four subjects. The mean maximal excretion of nickel in the urine was found during the first eight hours after nickel ingestion. In one subject the excretion was higher during the 4 p.m. to midnight period, and in another subject the maximal excretion was after midnight.

The average increase in serum concentration 2.5 hrs after nickel ingestion was 21 times (1.15 to 70), while the average increase in nickel urine excretion from day 1 to day 2 (comparing the periods 8:00 a.m. to 4:00 p.m.) was 65 times (6.3 to 153.6). The nickel concentrations listed in table I show great individual variations in the three types of fluids investigated in relation to nickel ingestion. Subjects no. 2

* Instrumentation Laboratory Inc.

FIGURE 1. Mean values of nickel in serum, whole blood and nickel excretion in urine in three following days in eight healthy volunteers. On day 2 at 8:00 a.m., the subjects ingested 5.6 mg nickel.



and in particular 6 attain extremely high values in all three parameters studied. The two males and females no. 1 and 5 showed a relatively small rise of nickel in serum and whole blood, whereas their nickel excretion in urine was clearly elevated. To illustrate the duration of excretion of nickel in urine, the values for day 3, midnight to 8:00 a.m., are also listed in table I. The excretion of nickel in the urine was still significantly elevated 40 to 48 hours after nickel ingestion as compared to the excretion before nickel ingestion.

With the assumption that the investigated values follow a normal distribution, there was no significant difference between nickel concentrations in serum or whole blood on day 2 at 8:00 a.m. and at 10:30 a.m. (Student's paired t-test). By the same statistical method on urine, comparing nickel excretion on day 1, 8:00 a.m. to 4:00 p.m. with that on day 2, 8:00 a.m. to 4:00 p.m., $p < 0.05$ was found. This lack of or low significance is due to the great standard deviations found in serum and whole blood on day 2, at 10:30 a.m. and in urine on day 2, 8:00 a.m. to 4:00 p.m. Assuming that the parameters do not follow a normal distribution and instead applying

the rank sum test, $p < 0.025$ was found in both serum, whole blood, and urine, which seems to agree more with the analysed values.

Before nickel ingestion on day 1 at 8:00 a.m., 1:00 and 3:30 p.m., and day 2 at 8:00 a.m., no correlation was found between the nickel concentration in serum and whole blood (corr. coeff. = 0.18; $p > 0.05$), and the concentrations varied considera-

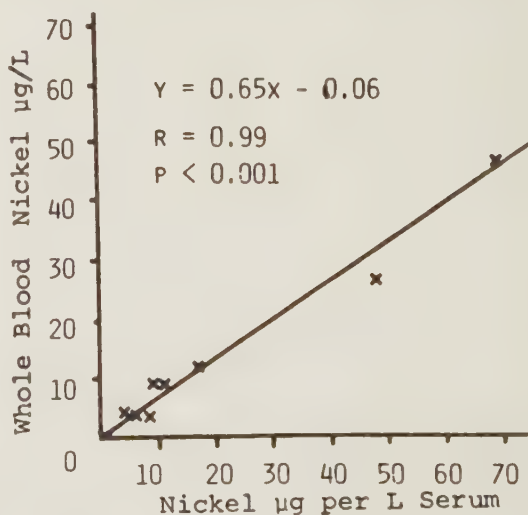


FIGURE 2. Correlation between nickel concentrations in serum and whole blood after ingestion of 5.6 mg nickel in eight healthy volunteers.

TABLE I

Nickel Concentrations in Serum, Whole Blood and Nickel Excretion in Urine Before and After Ingestion of 5.6 mg Nickel in Eight Healthy Volunteers

Subject Number	Day 1 Serum Ni $\mu\text{g/l}$			Day 2 Serum Ni $\mu\text{g/l}$			
	8:00	1:00	3:30	8:00	9:00	10:30	12:00
	a.m.	p.m.	p.m.	a.m.	a.m.	a.m.	a.m.
1	0.4		1.0	0.4	0.7	9.2	7.7
2	1.1		0.3	1.5	9.6	105.0	79.0
3	0.8	0.8	1.2	1.1	3.8	8.0	27.0
4	1.4	1.7	1.2	1.6	11.0	14.0	30.0
5	1.8	1.8	1.8	1.8	13.3	13.2	14.8
6	3.8	2.1	2.1	2.1	120.0	105.0	89.0
7	2.2	7.5	3.4	3.9	4.9	4.5	8.6
8		2.2	2.0	1.6	10.5	12.7	9.0
$\bar{X} \pm S$	1.64 $\pm$ 1.10	2.68 $\pm$ 2.41	1.60 $\pm$ 0.93	1.75 $\pm$ 1.01	21.7 $\pm$ 39.9	33.9 $\pm$ 43.9	33.1 $\pm$ 32.6

Subject Number	Day 1 Whole Blood Ni $\mu\text{g/l}$			Day 2 Whole Blood Ni $\mu\text{g/l}$			
	8:00	1:00	3:30	8:00	9:00	10:30	12:00
	a.m.	p.m.	p.m.	a.m.	a.m.	a.m.	a.m.
1	4.0		0.4	0.3	0.3	2.9	3.4
2	0.3		5.8	0.4	3.7	79.0	37.0
3	1.0	1.5	2.3	2.0	14.0	15.0	15.0
4	2.0	1.0	1.2	2.0	6.1	22.0	21.0
5	5.2	3.5	5.6	2.2	9.5	6.1	9.1
6	4.8	7.4	6.5	8.2	72.0	72.0	62.0
7	3.5	2.5	2.0	2.5	3.5	3.5	5.5
8	3.0	2.5	2.5	1.5	3.5	5.0	4.0
$\bar{X} \pm S$	2.98 $\pm$ 1.76	3.06 $\pm$ 2.29	3.29 $\pm$ 2.33	2.39 $\pm$ 2.49	14.1 $\pm$ 23.8	25.7 $\pm$ 31.5	19.6 $\pm$ 20.5

Subject Number	Day 1 Urine Ni Excretion μg			Day 2 Urine Ni Excretion μg		Day 3 Urine Ni Excretion μg
	8:00-4:00	4:00-00	00-8:00	8:00-4:00	8:00-8:00	00-8:00
	a.m. p.m.	p.m.	a.m.	a.m. p.m.	a.m. a.m.	a.m.
1	2.8	3.1	1.7	17.7	38.8	5.0
2	3.4	6.4	1.0	80.0	243.8	12.8
3	1.2	0.8	5.4	27.7	52.4	16.2
4	0.6	0.9	1.6	92.2	190.6	24.5
5	1.8	1.2	1.4	55.6	110.3	17.3
6	1.7	1.3	1.8	202.0	438.4	31.2
7	0.7	0.7	5.7	49.2	87.7	10.5
8	0.3	0.9	2.5	31.1	97.4	9.6
$\bar{X} \pm S$	1.56 $\pm$ 1.09	1.91 $\pm$ 1.97	2.64 $\pm$ 1.85	69.56 $\pm$ 59.4	157.4 $\pm$ 133.0	15.9 $\pm$ 8.51

bly during 24 hours in some subjects in both serum and whole blood. After nickel ingestion a positive correlation was found between nickel concentrations in serum and whole blood; the equation of the regression line, correlation coefficient, and *p* values are illustrated in figure 2.

The result also demonstrated a positive correlation between nickel concentrations in serum and nickel excretion in the urine. The corresponding serum values and nickel urine excretion are plotted in figure 3, and the equation of the regression line together with correlation coefficient and the *p* values are indicated in the figure.

The semilogarithmic values of nickel concentrations in serum are plotted against time in figure 4 to calculate the half-life ($T_{1/2}$) of nickel. The equation of the regression line, correlation coefficient and *p* values together with $T_{1/2}$ are given in the figure. During this study $T_{1/2}$ was 11 hours.

During the three days study, none of the subjects showed or complained of any physical or psychical symptoms similar to nickel intoxication, not even subjects no. 2 and no. 6 with high blood levels.

Discussion

Nickel concentrations found in blood and urine in this study before ingestion of nickel are of the same size as earlier found and reviewed by Bernacki et al in 1980.²

The results clearly show great variations of nickel concentrations in blood and nickel excretion in urine, even if the subjects ingested the same amount of nickel. Probably these differences are due to variations in absorption. Many factors such as general health, blood perfusion, and emptying time of the stomach, bile excretion and intake of different foods and liquids may influence the rate and completeness of absorption. In the present study, the effect of these factors was minimized by standardizing the method as far as possible.

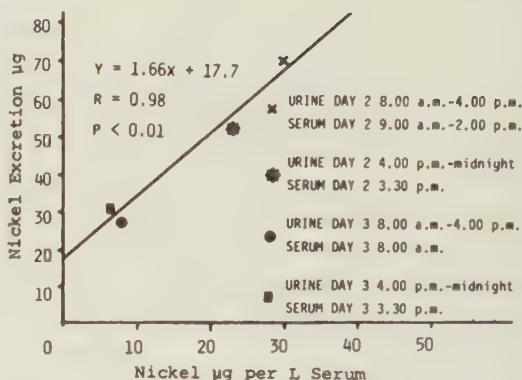


FIGURE 3. Correlation between nickel concentrations in serum and excretion of nickel in urine after ingestion of 5.6 mg nickel in eight healthy volunteers.

From a dermatological point of view, this great variation in nickel absorption is of great interest. It certainly explains the generalized vigorous clinical reactions to oral provocations seen in some patients⁴ to the "standard" dose of 5.6 mg, as well as reactions to a much smaller dose in others.^{4,10,18} Even the lack of reaction in a few patients to the dose of 5.6 mg may be a result of variation in absorption. It is even possible that the nickel sensitive patients with a chronic hand eczema of the pompholyx type³ absorb nickel to a greater extent than other nickel sensitive patients. However, the eczematous reactions seen in connection with oral provocation of nickel are probably not only dependant of absorption and concentration of nickel in the blood, but also of the immunological status of the patient.

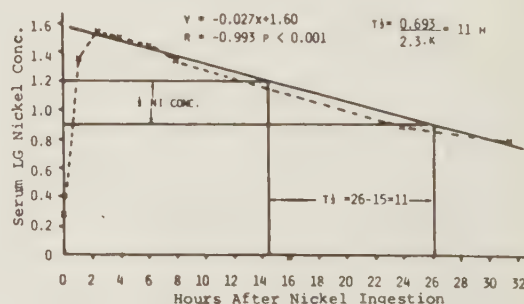


FIGURE 4. Nickel concentrations in serum after ingestion of 5.6 mg nickel (semilogarithmic diagram).

Menné et al¹⁴ have studied nickel excretion in the urine in six females and seven males on three consecutive days with the same nickel dose of 5.6 mg given orally. The results showed great individual variations but none of the 13 patients reached the level of excretion observed in some subjects of the present study. Their subjects were not healthy, but were patients with psoriasis and leg ulcers. The mean age was quite higher, and the intake of nickel in relation to food was not stated; therefore, the two studies can hardly be compared.

Earlier the concentration of serum nickel was two hours after ingestion of 5.6 mg nickel, and the nickel excretion in urine up to 7 hours after ingestion in 13 healthy volunteers. Also in that study it was found that there were great individual variations in serum nickel concentrations, whereas nickel excretion in the urine only was slightly elevated. During that study the subjects spent two 30 minute periods in a 75°C dry sauna bath, and for that reason the observed values can not be compared.

Bernacki et al² found a certain correlation between nickel concentrations in the air and end of work-shift urine in eight men working in an electroplating shop, but no correlation to nickel in prework-shift or midwork-shift urine. In another study,¹ there was no correlation between nickel concentrations in the air and urine. In eight of 12 analysed midwork-shift urines, the nickel amount was higher than in the pre- and endwork-shift urine. It is possible that the workers studied ingested and absorbed nickel contaminated food which may influence the nickel levels. Several factors influence the amount of nickel ingested and absorbed.³ For that reason analysis of nickel in body fluids during different types of nickel exposure, would probably result in a higher degree of precision and correlation if the methodological circumstances with respect to nickel ingestion were standardized as far as pos-

sible. On the other hand, Tola et al²⁰ found a close relationship between air nickel concentrations and urine and plasma nickel in four electroplating workers.

Before nickel ingestion no correlation was found by the present authors between nickel concentrations in serum and whole blood; however, after ingestion of nickel the correlation was good. It is known that iron interferes with nickel in electrothermal atomic absorption spectrophotometry and this interference increases with decreasing concentration of nickel. This may explain the absence of correlation before nickel ingestion. It seems that analysis of nickel in whole blood hardly gives any advantages compared to that of serum.

The results quite obviously showed that the kidneys have a high capacity of excreting nickel. The maximal renal nickel excretion in this study, as illustrated in subject no. 6, is close to 0.5 mg per day. The good correlation between serum nickel concentrations and nickel urine excretion together with the pattern of the curves in figure 1 seem to indicate that nickel is excreted in the urine proportionally to the serum concentration. In studies in different rodents,^{7, 16, 17, 21} there was a rapid urinary excretion of nickel during the first one or two days, and this corresponds with the findings in this study.

The semilogarithmic curve of serum nickel concentrations and its regression line, with a correlation coefficient numerically close to one, indicate that the excretion of nickel seems to follow a first-order kinetic reaction. Onkelinx et al¹⁶ have described in mathematical terms a compartmental model which suggests that nickel in rats and rabbits is diluted within a volume of two compartments but eliminated by a first-order kinetic reaction. During the first two days after i.v. injection of radioactive nickel chloride into rabbits, van Soestbergen et al²² found $T_{1/2} = 8.2$ hours; however, four to seven days after injection, $T_{1/2}$ was 95 hours. In this

study, $T_{1/2}$ was 11 hours, 1 to 32 hours after ingestion of nickel. Samples of serum and urine taken later than in the present study are required to see if $T_{1/2}$ is also prolonged with time in human beings.

The present study shows that analysis of nickel in both urine and serum reflects ingestion of a soluble nickel salt. Urine, however, seems to be the most reliable type of sample to investigate. The nickel excretion in urine up to eight hours after ingestion or probably just one sample collected after 5 to 10 hours should be sufficient to register this type of exposure. Of course only one sample collecting procedure will minimize the individual inconvenience, as well as reduce the risks of contamination and the costs of the investigation.

This study may provide some basic understanding of the metabolism of ingested nickel, useful when studying the relationship between nickel exposure and eczematous activity and also the effect of different nickel chelating compounds.

Acknowledgment

The authors are grateful to Björn Edman for skillful statistical assistance.

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MICROMORPHOLOGY AND SPECIFICITY OF ORALLY INDUCED
FLARE-UP REACTIONS IN NICKEL SENSITIVE PATIENTS

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Abstract. Micromorphology and specificity of orally induced flare-up reactions of 4-7 weeks old nickel patch test sites compared to control test sites with tuberculin and benzalkonium were investigated in nickel sensitive patients with pompholyx. Of the test sites only that of nickel flared after ingestion of nickel as did the hand eczema. The clinical picture and light microscopical findings agreed and were both eczematous.

Key words: Nickel allergy; Hand eczema; Flare-up reactions; Micromorphology

INTRODUCTION

Ingested nickel activates the hand dermatitis in nickel sensitive patients (4, 5, 9, 10). Even flare-up reactions of earlier patch test or contact dermatitis sites along with a maculo-papular rash on the abdomen, elbow flexures and sides of neck have been described in nickel sensitive patients following ingestion of nickel (4, 5).

From a pathogenetic point of view flare-up reactions are interesting and until now the nature of these reactions has not been investigated in man. The following study was undertaken to investigate the micromorphology and specificity of flare-up reactions in nickel sensitive females. The study was carried out on specific and non-specific patch tests as well as on the hand eczema proper.

MATERIAL AND METHODS

Patients

The study was performed on 5 female patients 27-50 years of age. They were all hypersensitive to nickel proved by previous patch testing and they had a history of metal sensitivity since several years. The patients had a periodic hand eczema of the pompholyx type (3).

Tests

Patch testing (Finn chambers) was carried out on the buttocks (Fig. 1). Nickel sulfate 5% in petrolatum was applied in duplicate. As controls served a single intradermal test with tuberculin 2 TU (purified protein derivative, PPD, Statens Seruminstitut, Copenhagen, Denmark) and duplicate patch tests with benzalkonium chloride 1.0% in aqueous solution. The patch tests were removed by the patients after 48 hours or earlier in the case of itch or pain. All tests were read 72 hours after application at which time the margins of the test reactions were thoroughly marked with a fuchsin-silver nitrate ink. In one patient the concentration of tuberculin and benzalkonium chloride had to be increased to 5 TU and 2.0%, respectively, because of negative reactions; in this case even 5 TU tuberculin was negative. In another patient the nickel test was negative on the buttocks; subsequent patch tests on the upper arms, however, were clearly positive. With these exceptions all tests resulted in obvious inflammatory reactions. During the following weeks until provocation the patients maintained the marking themselves and were not allowed to use any topicals on the test areas.

Provocation

The patients were admitted to the ward 4-7 weeks after testing. At clinical examination the infiltration of all tuberculin and benzalkonium reactions had disappeared. In 2 patients - those examined 4 weeks after testing - a slight erythema and infiltration remained in the nickel test areas but no residues were observed in the other 3 patients. The pompholyx was more or less active in 4 patients but inactive in one.

Punch biopsies, 2 mm diameter, for light microscopy and for direct immunofluorescence (IF) were taken from the center of the marked test areas (from the nickel and benzalkonium sites of the left buttock). Biopsies for the same purposes were obtained from the left hypothenar region, an area of usual vesicular activity, not however at the time of examination.

The patients were given a capsule containing 25 mg nickel sulfate ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) with a nickel content of 5.6 mg. During the following 24 hours the patients were repeatedly examined. At the end of the 24 hours a new set of punch biopsies were taken from contralateral but equivalent skin areas of the buttocks and palms; for the tuberculin reaction the one and only area was used.

Histopathological examination

The biopsy material was immediately fixed in 10% buffered formalin solution. After histotechnical preparations, the 3-4 um thick sections were stained according to the following methods: haematoxylin-eosin, Giemsa, toluidine blue, McManus, and Weigerts elastin stain.

Direct immunofluorescence

The specimens were quickly frozen or preserved in a transport medium described by Michel (10) for a few hours before they were frozen in a mixture of propane-butane to the temperature of liquid nitrogen. Cryostate sections were incubated with fluorescein-labelled antisera from rabbit anti-human IgG, IgA, IgM, complement 3 and fibrinogen (purchased from DAKO Immuno-globulins Ltd., Copenhagen, Denmark) and examined according to the technique detailed by Beutner et al (2).

RESULTS

Clinical reactions

In all 5 patients the nickel patch tests flared after oral provocation. The patients noticed itching of the test areas 4-10 hours after nickel ingestion and at 10 hours erythema and some infiltration could be observed. At 24 hours there was a strong eczematous reaction with erythema, infiltration, papules and/or vesicles on an area 2-3 times larger than the original patch test. One patient patch tested with nickel on her upper left arm 4 months before challenge reacted with an intense eczematous flare in that site as well as in the patch tests on her buttock. The intensity of the flare reactions was independent of the time interval between patch test and provocation. No clinical reaction whatsoever was observed in the former tuberculin and benzalkonium test sites.

Four patients noticed itch in their palms 8-10 hours after nickel ingestion and at 24 hours there was an increased vesicular response in the palms. The fifth patient had palmar

itch only but no visible change. In addition, all patients flared on a few earlier sites of contact dermatitis such as earlobes or left wrist. A maculo-papular eruption, mainly on neck and abdomen occurred in 3 of the 5 patients. It appeared already after 3-4 hours and intensified during the next 20 hours.

Histopathological examination

In the preprovocational test biopsies there was no or only slight inflammatory reaction with slight dermal oedema and a few lymphocytes. No difference was observed between the 3 different tests (nickel, tuberculin, benzalkonium chloride) and the palm in this respect (Fig. 2 and Fig. 4). In the surroundings of the superficial dermal vessels scattered mast cells filled with metachromatic granula were observed. There was no epidermal spongiosis or vesicular formation.

In the biopsies taken from the benzalkonium chloride and tuberculin tests 24 hours after oral nickel provocation no difference compared to biopsies taken the day before was observed.

In most biopsies taken from the nickel tests and the palm 24 hours after provocation striking histological changes compared to preprovocational biopsies were found. There was a marked dermal oedema and a strong lymphocytic reaction around the superficial dermal vessels. Only few polymorphonuclears were observed and no difference between pre- and postprovocational biopsies was found in this respect. There was also a marked epidermal reaction with spongiosis and in some cases a pronounced formation of vesicles and/or bullae (Fig. 3 and Fig. 5). Some metachromatic granula outside mast cells were observed.

Immunofluorescence examination

No significant findings of IgG, IgA, IgM, complement 3 or fibrinogen were observed when the specimens taken before and after provocation with nickel were compared using the direct immunofluorescence technique.

DISCUSSION

Clinically, more or less pronounced eczematous reactions with erythema, infiltration, papules and/or vesicles were observed in 4-7 weeks old nickel patch tests in all 5 patients 24 hours after oral provocation with nickel. Besides flare of nickel patch test sites the patients also flared on earlier sites of contact dermatitis. Three patients were certain that they had had no dermatitis for the last 2-4 years in these areas. Assessed from the different time intervals between patch testing or previous contact dermatitis reactions and oral nickel provocation, we can conclude that flare-up reactions in such sites can be provoked 4 weeks - 4 years later. The time interval between the original eczema and the flare-up reaction in humans thus can be longer than that in guinea pigs. In this animal flare-up reactions were consistently provoked 2 weeks after patch testing but not after 3 months (12).

The benzalkonium chloride and tuberculin tests were chosen as examples of a toxic dermatitis and of a delayed-type hypersensitivity reaction, respectively. Neither was reactivated indicating that the oral antigen had no effect on the inflammatory process per se, nor on another type IV reaction than nickel allergy. No patient with nickel allergy and pompholyx plus another

non-related contact allergy was available for study. Apart from this, our provocation study speaks in favour of a specific activation by the antigen in question.

The result of the light microscopic examination agrees with the reactions observed clinically. The histopathological reactions both in the palms and in the nickel patch test sites with dermal oedema, perivascular lymphocytic infiltration and epidermal spongiosis/vesicles observed after oral nickel provocation were clearly eczematous. The absence of any particular histopathological changes at the tuberculin and benzalkonium test sites also agrees with the absence of clinical reactions.

The histological findings in flare-up reactions of guinea pigs with a dense infiltrate of polymorphonuclear leukocytes described by Polák & Turk (12) do not agree with the result of the present study. In fact, only few polymorphonuclear leukocytes were found in the flare-up reactions of the nickel sensitive females. Rather more, the dermal picture resembled that described during the spontaneous flare-up in man in DNCB sensitization (14).

It can be suspected that the mast cells play some role in the flare-up reactions investigated. Metachromatic granula were observed outside the mast cells and a degranulation seemed to have occurred. Dvorak et al (8) have in detail studied delayed hypersensitivity reactions in humans and found mast cells present in increased numbers compared to controls. Mast cell degranulation was suspected when observed by light microscopy but more precisely demonstrated by electron microscopy. Even if the flare-up reactions studied by us are induced in another way than regular contact dermatitis (patch test reaction) and therefore hardly can be compared, it is

noteworthy that mast cell degranulation also was observed. One can only speculate on the role of mast cells in human delayed hypersensitivity and flare-up reactions. Specific sensitized lymphocytes or their lymphokines may attract and degranulate mast cells (7) inducing dermal oedema, erythema and increased cellular inflammatory exsudate. The fact that the flare-up reactions were more intense and oedematous than the original patch test reactions may speak in favour of the mast cell degranulation playing some active part in this reaction.

Basophil leukocytes have been observed in increased numbers in delayed hypersensitivity reactions in man (1, 6, 7, 15). However, the histopathological method applied in the present study did not reveal any basophil leukocytes.

Neither immunoglobulins of the IgG, IgA and IgM class, nor complement 3 and fibrinogen were found in the flare-up reactions. Polák et al (13) believe that flare-up reactions in guinea pigs are mediated by humoral antibodies formed and/or released by sensitized lymphocytes in the patch test site. In the present study samples were taken at one time interval only which might give a false negative result. With this reservation, our results speak against a pathogenetic role of humoral antibodies in the type of flare-up reactions examined. Possibly, such antibodies or immune complexes might be of importance for the appearance of the maculo-papular eruptions observed in connection with oral nickel provocation (4, 5).

Intense flare-up reactions of patch test sites or earlier contact dermatitis reactions are usually not presented by nickel sensitive patients at examination. We now have shown

that the pompholyx type of hand eczema, so common in females with nickel allergy, reacts in a similar way clinically and histopathologically to oral provocation as the flare-up reactions mentioned. They are all true secondary eruptions and further studies on their micromorphologic and immunopathogenic dynamics are certainly warranted.

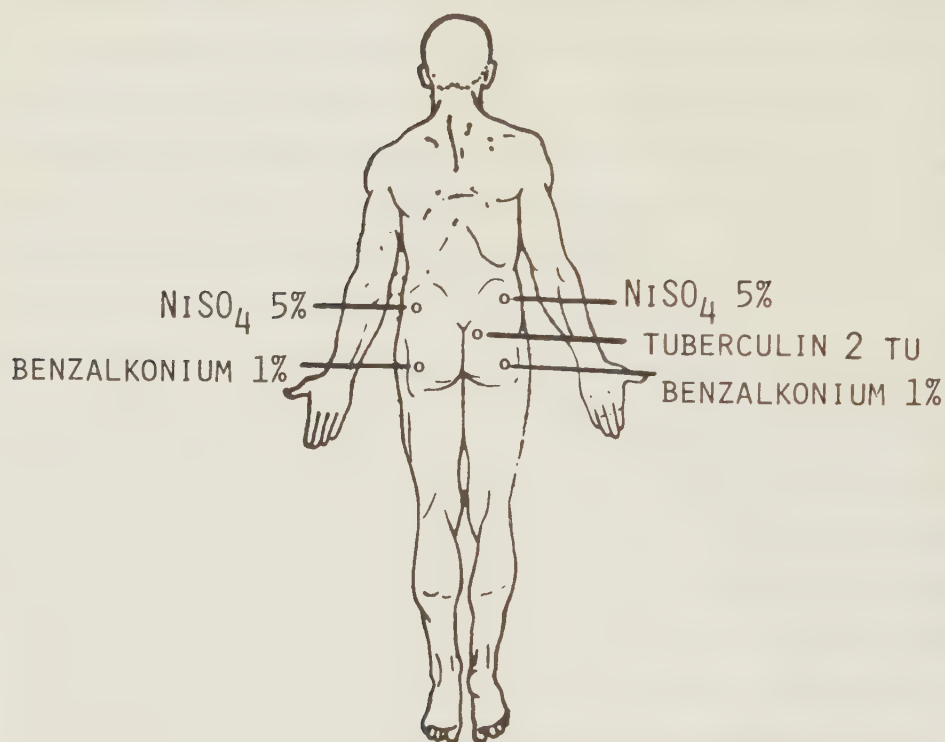


Fig. 1. Localization on the buttocks of patch tests with nickel sulfate and benzalkonium chloride and intradermal test with tuberculin 4-7 weeks before oral provocation.

Figure 2. Skin from left buttock immediately before oral nickel provocation. Almost normal histological appearance of the epidermis and the dermis. There are a few lymphocytes in the perivascular zones of the dermis. No spongiosis or spongiotic vesicles in the epidermis. Htx-eos x 128.

Figure 3. Skin from the same patient and the same but contralateral localization as in Fig. 2 24 hours after oral nickel provocation. There is a marked spongiosis with spongiotic vesicles in the epidermis and some coagulated exsudate on the epidermal surface. In the upper dermis there is a perivascular oedema and a cellular exsudate consisting mainly of lymphocytes. In the vicinity of the basal epidermis there are lymphocytes some of which are beginning to infiltrate the epidermis. Htx-eos x 128.

Figure 4. Palmar skin from another nickel allergic patient immediately before oral provocation. There is some parakeratosis and only slight perivascular lymphocytic infiltration. No spongiosis or spongiotic vesicles. Htc-eos 128.

Figure 5. Palmar skin (contralateral) from the same patient as in Fig. 4 24 hours after oral nickel provocation. The histological picture of an acute eczematous dermatitis with marked epidermal spongiosis and spongiotic vesiculation as well as perivascular infiltration of lymphocytes which are also seen at the basal epidermis. Htx-eos x 128.

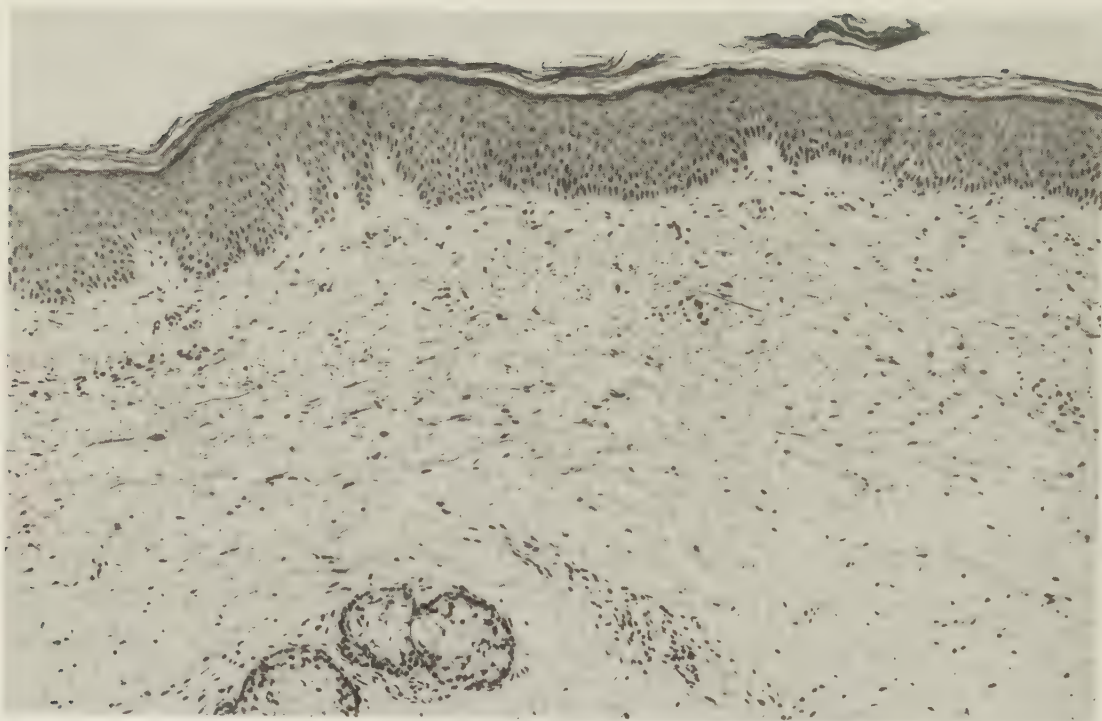


Fig. 2.

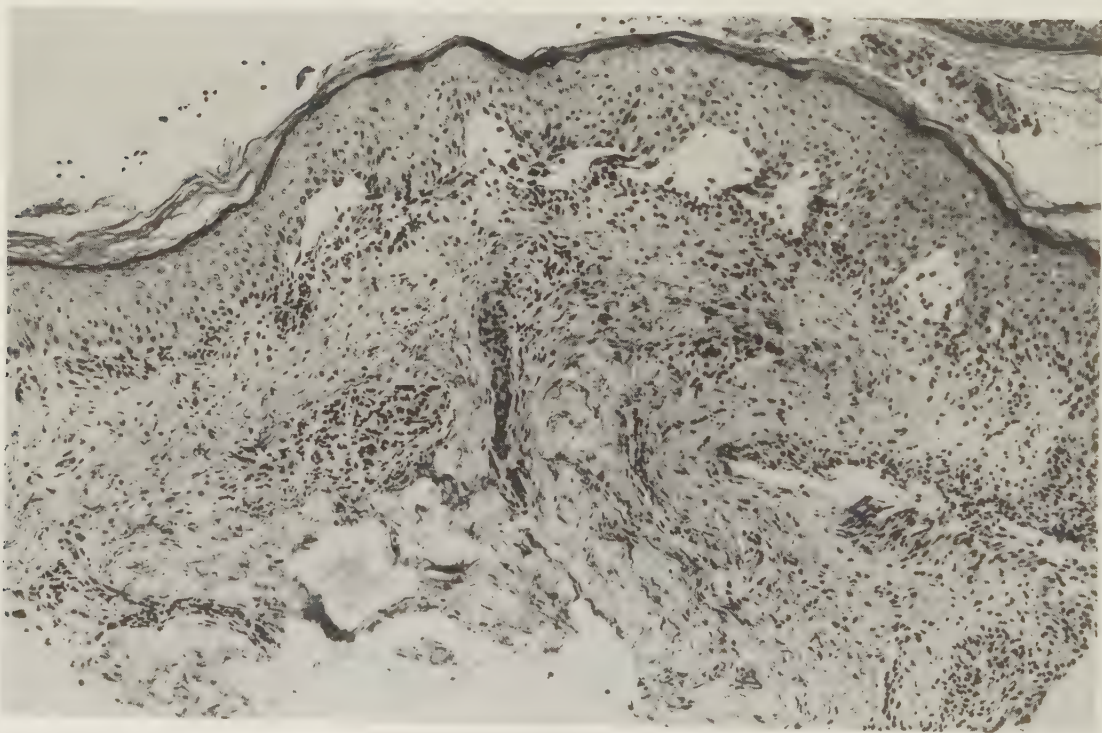


Fig. 3.

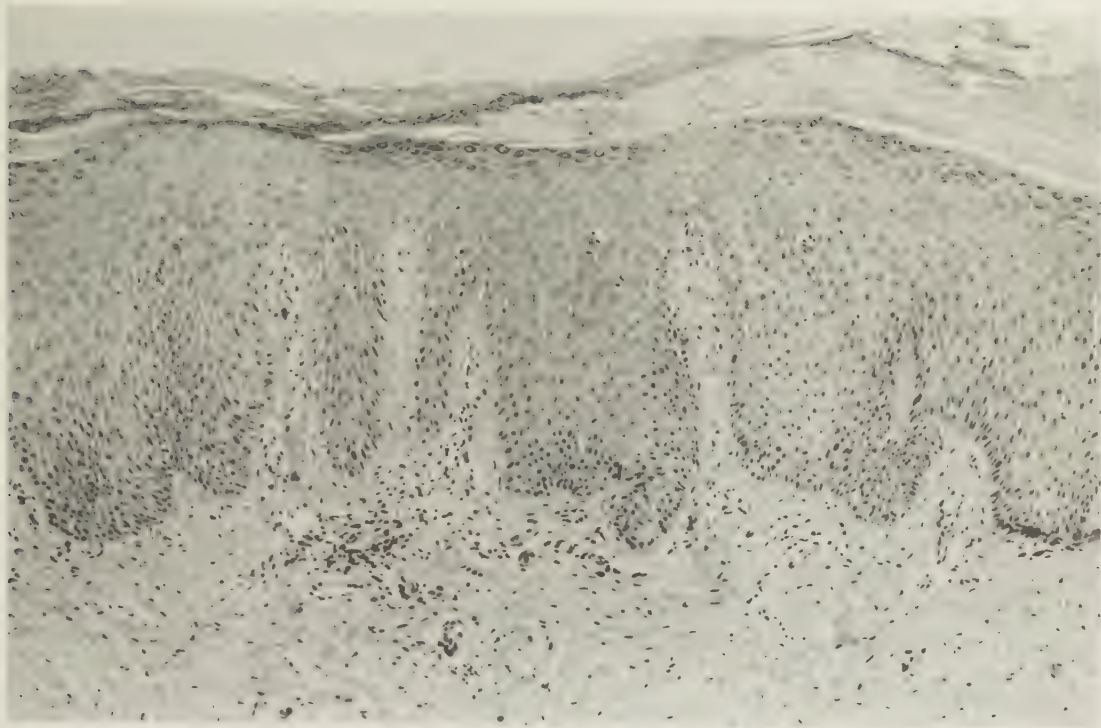


Fig. 4.

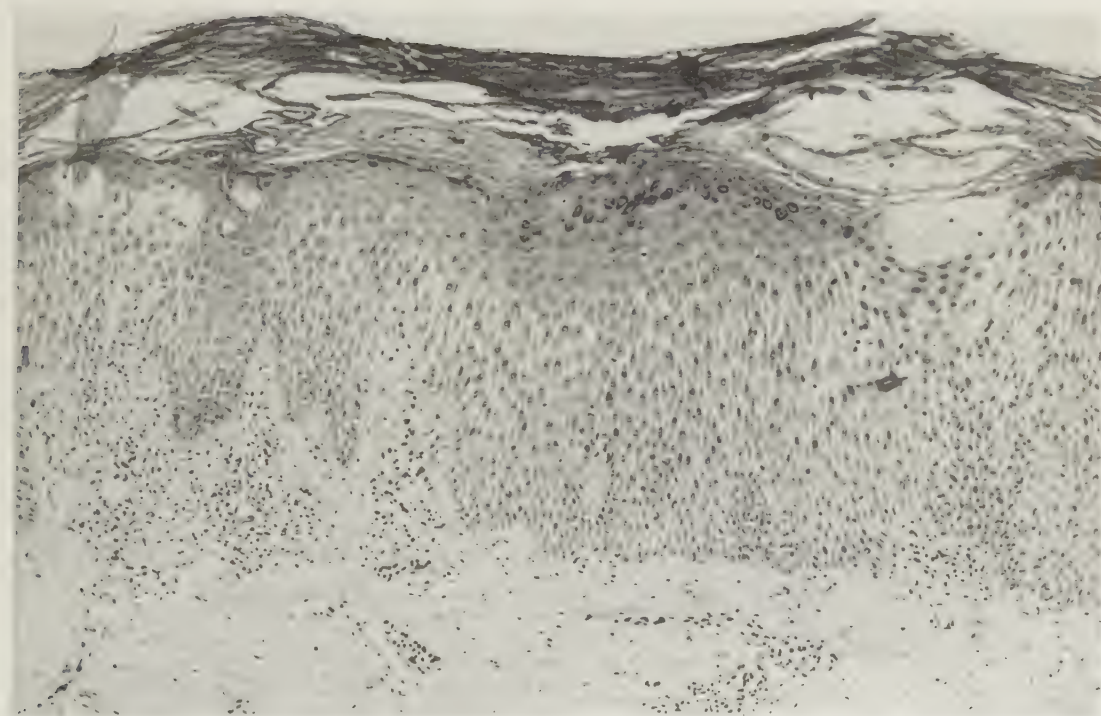


Fig. 5.

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